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<b>(21) International Application Number:</b> PCT/GB00/00162 <b>(22) International Filing Date:</b> 21 January 2000 (21.01.2000) <b>(30) Priority Data:</b> 9901444.1 23 January 1999 (23.01.1999) GB <b>(60) Parent Application or Grant</b> BRITISH BIOTECH PHARMACEUTICALS LIMITED [/]; () . AYSCOUGH, Andrew, Paul [/]; (). WHITTAKER, Mark [/]; (). AYSCOUGH, Andrew, Paul [/]; (). WHITTAKER, Mark [/]; (). WALLS, Alan, J. ; ().	<b>Published</b>	
<b>(54) Title: ANTI-INFLAMMATORY AGENTS</b> <b>(54) Titre: AGENTS ANTI-INFLAMMATOIRES</b>  <b>(57) Abstract</b> <p>Compounds of formula (I) wherein <math>R_{\text{L}}4</math> is an ester or thioester group, and R, <math>R_{\text{L}}1</math>, <math>R_{\text{L}}2</math> and <math>R_{\text{L}}3</math> are as defined in the specification, inhibit intracellular leukotriene-<math>A_{\text{L}}4</math> hydrolase activity and have anti-inflammatory activity.</p> <b>(57) Abrégé</b> <p>Cette invention concerne des composés représentés par la formule (I) dans laquelle <math>R_{\text{L}}4</math> est un ester ou un groupe thioester, et R, <math>R_{\text{L}}1</math>, <math>R_{\text{L}}2</math> et <math>R_{\text{L}}3</math> sont conformes à la spécification du descriptif. Ces composés inhibent l'activité hydrolase leukotriène-<math>A_{\text{L}}4</math> intracellulaire et ont une action anti-inflammatoire.</p>		

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(54) Title: ANTI-INFLAMMATORY AGENTS			
<div style="text-align: center;"> <p>(I)</p> </div>			
(57) Abstract			
Compounds of formula (I) wherein R <sub>4</sub> is an ester or thioester group, and R, R <sub>1</sub> , R <sub>2</sub> and R <sub>3</sub> are as defined in the specification, inhibit intracellular leukotriene-A <sub>4</sub> hydrolase activity and have anti-inflammatory activity.			

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**Description**

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## Anti-Inflammatory Agents

The present invention relates to the use of certain esters and thioesters for the treatment of diseases responsive to inhibition of intracellular leukotriene-A<sub>4</sub> hydrolase activity.

### Background to the Invention

The leukotriene cascade of arachadonic acid is a key mechanism in many inflammatory and allergic disease states. The dihydroxy fatty acid leukotriene B<sub>4</sub> (LTB<sub>4</sub>), produced by this cascade, is a key pro-inflammatory mediator. LTB<sub>4</sub> stimulates adhesion of circulating neutrophils to vascular endothelium, directs their migration toward sites of inflammation, and induces secretion of further inflammatory mediators. (For reviews see R.A. Lewis et al, N. Engl. J. Med. 1990, 323, 645-655 and M. -Q. Zhang, Curr. Med. Chem. 1997, 4, 67-78.) Leukotriene-A<sub>4</sub> hydrolase (LTA<sub>4</sub>-hydrolase) (EC 3.3.2.6) is an enzyme that catalyses the final and rate limiting step in the synthesis of LTB<sub>4</sub>. Inhibition of LTA<sub>4</sub> hydrolase selectively blocks the biosynthesis of LTB<sub>4</sub> which may provide an advantage over current inhibitors, such as those of 5-lipoxygenase, that block earlier in the leukotriene cascade and as a result are less selective.

Disease states associated with elevated levels of LTB<sub>4</sub>, and which are therefore considered to be responsive to inhibition of intracellular leukotriene-A<sub>4</sub> hydrolase activity include asthma, inflammatory bowel disease, psoriasis and arthritis.

Peptidomimetic compounds, such as bestatin, captopril and kelatorphan exhibit LTA<sub>4</sub> hydrolase inhibitory activity against isolated enzyme (T.D. Penning et al, Biorg. Med. Chem. Lett., 1995, 5, p2517-2522). However, these compounds are unable to effectively penetrate cells and hence have little anti-inflammatory activity. There is therefore a need in the art for compounds which are capable of inhibiting intracellular LTA<sub>4</sub> hydrolase activity.

Brief Description of the Invention

This invention is based on the finding that certain esters and thioesters containing an N-formyl hydroxylamine group are capable of inhibiting intracellular LTA<sub>4</sub> hydrolase activity, resulting in efficient attenuation of LTB<sub>4</sub> biosynthesis. Those esters and thioesters are therefore of use for the treatment of diseases responsive to such inhibition, for example inflammatory and allergic conditions including asthma, rheumatoid arthritis, osteoarthritis, multiple sclerosis, ulcerative colitis, contact and atopic dermatitis, psoriasis, inflammatory bowel disease and Crohn's disease.

The following patent publications disclose compounds containing an N-formyl hydroxylamine group which are stated to be inhibitors of matrix metalloproteinases (MMPs), and thus potentially of value for the treatment of diseases involving inappropriate degradation of the extracellular matrix. However, few examples of such compounds have been specifically made and described those publications:

EP-B-0236872	(Roche)
WO 92/09563	(Glycomed)
WO 92/04735	(Syntex)
WO 95/19965	(Glycomed)
WO 95/22966	(Sanofi Winthrop)
WO 95/33709	(Roche)
WO 96/23791	(Syntex)
WO 96/16027	(Syntex/Agouron)
WO 97/03783	(British Biotech)
WO 97/18207	(DuPont Merck)

Brief Description of the Invention

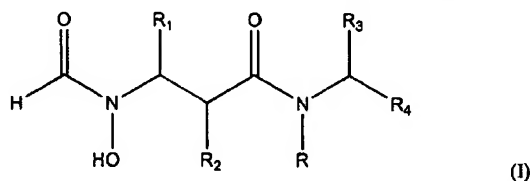
This invention is based on the identification of a class of ester and thioester compounds containing an N-formyl hydroxylamine group, which are capable of inhibiting intracellular LTA<sub>4</sub> hydrolase activity, resulting in efficient attenuation of LTB<sub>4</sub> biosynthesis. Those esters and thioesters are therefore of use for the treatment

of diseases responsive to such inhibition, for example inflammatory and allergic conditions including asthma, rheumatoid arthritis, osteoarthritis, multiple sclerosis, ulcerative colitis, contact and atopic dermatitis, psoriasis, inflammatory bowel disease and Crohn's disease.

The ester and thioester compounds in question have certain structural similarities to known MMP inhibitors generically disclosed in the foregoing patent publications. Most of those prior art publications are concerned with amides rather than esters or thioesters group, but a few (WO 92/09563, WO 95/19965 and WO 95/22966) include within their generic disclosure compounds having a carboxylate ester group in place of the amide group. The carboxylate ester compounds with which this invention is concerned thus represent a selection of a notional subclass from the compounds proposed in the art as MMP inhibitors or for other purposes, for a specific and previously unrecognised pharmaceutical utility - inhibiting intracellular LTA<sub>4</sub> hydrolase activity.

#### Detailed Description of the Invention

In its broadest aspect, the present invention provides a method for treatment of mammals suffering diseases responsive to inhibition of intracellular leukotriene-A<sub>4</sub> hydrolase activity, comprising administering to the mammal suffering such disease an amount of a compound of general formula (I) or a pharmaceutically acceptable salt hydrate or solvate thereof sufficient to inhibit such activity:



wherein

R is hydrogen or (C<sub>1</sub>-C<sub>6</sub>)alkyl;

R<sub>1</sub> is hydrogen;

(C<sub>1</sub>-C<sub>6</sub>)alkyl;

(C<sub>2</sub>-C<sub>6</sub>)alkenyl;

phenyl or substituted phenyl;

phenyl (C<sub>1</sub>-C<sub>6</sub>)alkyl or substituted phenyl(C<sub>1</sub>-C<sub>6</sub>)alkyl;

phenyl (C<sub>2</sub>-C<sub>6</sub>)alkenyl or substituted phenyl(C<sub>2</sub>-C<sub>6</sub>)alkenyl

heterocyclyl or substituted heterocyclyl;

heterocyclyl(C<sub>1</sub>-C<sub>6</sub>)alkyl or substituted heterocyclyl(C<sub>1</sub>-C<sub>6</sub>)alkyl;

a group BSO<sub>n</sub>A- wherein n is 0, 1 or 2 and B is hydrogen or a (C<sub>1</sub>-C<sub>6</sub>) alkyl, phenyl, substituted phenyl, heterocyclyl substituted heterocyclyl, (C<sub>1</sub>-C<sub>6</sub>)acyl, phenacyl or substituted phenacyl group, and A represents (C<sub>1</sub>-C<sub>6</sub>)alkylene;

amino(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkylamino(C<sub>1</sub>-C<sub>6</sub>)alkyl, di(C<sub>1</sub>-C<sub>6</sub>)alkylamino(C<sub>1</sub>-C<sub>6</sub>)alkyl, hydroxy(C<sub>1</sub>-C<sub>6</sub>)alkyl, mercapto(C<sub>1</sub>-C<sub>6</sub>)alkyl or carboxy(C<sub>1</sub>-C<sub>6</sub>) alkyl wherein the amino-, hydroxy-, mercapto- or carboxyl-group are optionally protected or the carboxyl- group amidated;

lower alkyl substituted by carbamoyl, mono(lower alkyl)carbamoyl, di(lower alkyl)carbamoyl, di(lower alkyl)amino, or carboxy-lower alkanoylamino; or

a cycloalkyl, cycloalkenyl or non-aromatic heterocyclic ring containing up to 3 heteroatoms, any of which may be (i) substituted by one or more substituents selected from C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, halo, cyano ( -CN), -CO<sub>2</sub>H, -CO<sub>2</sub>R, -CONH<sub>2</sub>, -CONHR, -CON(R)<sub>2</sub>, -OH, -OR, oxo-, -SH, -SR, -NHCOR, and -NHCO<sub>2</sub>R wherein R is C<sub>1</sub>-C<sub>6</sub> alkyl or benzyl and/or (ii) fused to a cycloalkyl or



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heterocyclic ring;

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R<sub>2</sub> is a C<sub>1</sub>-C<sub>12</sub> alkyl,

C<sub>2</sub>-C<sub>12</sub> alkenyl,

C<sub>2</sub>-C<sub>12</sub> alkynyl,

phenyl(C<sub>1</sub>-C<sub>6</sub> alkyl)-,

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heteroaryl(C<sub>1</sub>-C<sub>6</sub> alkyl)-,

phenyl(C<sub>2</sub>-C<sub>6</sub> alkenyl)-,

heteroaryl(C<sub>2</sub>-C<sub>6</sub> alkenyl)-,

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phenyl(C<sub>2</sub>-C<sub>6</sub> alkynyl)-,

heteroaryl(C<sub>2</sub>-C<sub>6</sub> alkynyl)-,

cycloalkyl(C<sub>1</sub>-C<sub>6</sub> alkyl)-,

cycloalkyl(C<sub>2</sub>-C<sub>6</sub> alkenyl)-,

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cycloalkyl(C<sub>2</sub>-C<sub>6</sub> alkynyl)-,

cycloalkenyl(C<sub>1</sub>-C<sub>6</sub> alkyl)-,

cycloalkenyl(C<sub>2</sub>-C<sub>6</sub> alkenyl)-,

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cycloalkenyl(C<sub>2</sub>-C<sub>6</sub> alkynyl)-,

phenyl(C<sub>1</sub>-C<sub>6</sub> alkyl)O(C<sub>1</sub>-C<sub>6</sub> alkyl)-, or

heteroaryl(C<sub>1</sub>-C<sub>6</sub> alkyl)O(C<sub>1</sub>-C<sub>6</sub> alkyl)- group,

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any one of which may be optionally substituted by

C<sub>1</sub>-C<sub>6</sub> alkyl,

C<sub>1</sub>-C<sub>6</sub> alkoxy,

halo,

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cyano (-CN),

phenyl or heteroaryl, or

phenyl or heteroaryl substituted by

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C<sub>1</sub>-C<sub>6</sub> alkyl,

C<sub>1</sub>-C<sub>6</sub> alkoxy,

halo, or

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cyano (-CN);

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$R_3$  is the characterising group of a natural or non-natural  $\alpha$  amino acid in which any functional groups may be protected; and

$R_4$  is an ester or thioester group,

or a pharmaceutically acceptable salt, hydrate or solvate thereof.

In another broad aspect of the invention, there is provided the use of a compound of formula (I) as defined in claim 1 in the preparation of a pharmaceutical or veterinary composition for treatment of mammals suffering diseases responsive to inhibition of intracellular leukotriene- $A_4$  hydrolase activity.

As used herein the term "( $C_1$ - $C_6$ )alkyl" or "lower alkyl" means a straight or branched chain alkyl moiety having from 1 to 6 carbon atoms, including for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl and n-hexyl.

The term "( $C_2$ - $C_6$ )alkenyl" means a straight or branched chain alkenyl moiety having from 2 to 6 carbon atoms having at least one double bond of either E or Z stereochemistry where applicable. This term would include, for example, vinyl, allyl, 1- and 2-butenyl and 2-methyl-2-propenyl.

The term " $C_2$ - $C_6$  alkynyl" refers to straight chain or branched chain hydrocarbon groups having from two to six carbon atoms and having in addition one triple bond. This term would include for example, ethynyl, 1-propynyl, 1- and 2-butylnyl, 2-methyl-2-propynyl, 2-pentylnyl, 3-pentylnyl, 4-pentylnyl, 2-hexynyl, 3-hexynyl, 4-hexynyl and 5-hexynyl.

The term "cycloalkyl" means a saturated alicyclic moiety having from 3-8 carbon atoms and includes, for example, cyclohexyl, cyclooctyl, cycloheptyl, cyclopentyl, cyclobutyl and cyclopropyl.

The term "cycloalkenyl" means an unsaturated alicyclic moiety having from 4-8 carbon atoms and includes, for example, cyclohexenyl, cyclooctenyl, cycloheptenyl, cyclopentenyl, and cyclobutenyl. In the case of cycloalkenyl rings of from 5-8 carbon atoms, the ring may contain more than one double bond.

The term "aryl" means an unsaturated aromatic carbocyclic group which is monocyclic (eg phenyl) or polycyclic (eg naphthyl).

The unqualified term "heterocyclyl" or "heterocyclic" means (i) a 5-7 membered heterocyclic ring containing one or more heteroatoms selected from S, N and O, and optionally fused to a benzene ring, including for example, pyrrolyl, furyl, thienyl, piperidinyl, imidazolyl, oxazolyl, thiazolyl, thiadiazolyl, pyrazolyl, pyridinyl, pyrrolidinyl, pyrimidinyl, morpholinyl, piperazinyl, indolyl, benzimidazolyl, maleimido, succinimido, phthalimido, 1,2-dimethyl-3,5-dioxo-1,2,4-triazolidin-4-yl, 3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl, 2-methyl-3,5-dioxo-1,2,4-oxadiazol-4-yl, 3-methyl-2,4,5-trioxo-1-imidazolidinyl, 2,5-dioxo-3-phenyl-1-imidazolidinyl, 2-oxo-1-pyrrolidinyl, 2,5-dioxo-1-pyrrolidinyl or 2,6-dioxopiperidinyl, or (ii) a naphththalimido (ie 1,3-dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl), 1,3-dihydro-1-oxo-2H-benz[f]isoindol-2-yl, 1,3-dihydro-1,3-dioxo-2H-pyrrolo[3,4-b]quinolin-2-yl, or 2,3-dihydro-1,3-dioxo-1H-benz[d,e]isoquinolin-2-yl group.

The term "heteroaryl" means a 5-7 membered substituted or unsubstituted aromatic heterocycle containing one or more heteroatoms. Illustrative of such rings are thienyl, furyl, pyrrolyl, imidazolyl, thiazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl.

The term "ester" or "esterified carboxyl group" means a group  $R_9O(C=O)-$  in which  $R_9$  is the group characterising the ester, notionally derived from the alcohol  $R_9OH$ .

The term "thioester" means a group  $R_9S(C=O)-$  or  $R_9S(C=S)-$  or  $R_9O(C=S)-$  in which  $R_9$  is the group characterising the thioester, notionally derived from the alcohol  $R_9OH$ .

or the thioalcohol  $R_9SH$ .

Unless otherwise specified in the context in which it occurs, the term "substituted" as applied to any moiety herein means substituted with up to four substituents, each of which independently may be  $(C_1-C_6)$ alkyl,  $(C_1-C_6)$ alkoxy, hydroxy, mercapto,  $(C_1-C_6)$ alkylthio, amino, halo (including fluoro, chloro, bromo and iodo), nitro, trifluoromethyl,  $-COOH$ ,  $-CONH_2$ ,  $-CN$ ,  $-COOR^A$ ,  $-CONHR^A$  or  $-CONHR^AR^A$  wherein  $R^A$  is a  $(C_1-C_6)$ alkyl group or the residue of a natural alpha-amino acid.

The term "side chain of a natural or non-natural alpha-amino acid" means the group  $R^1$  in a natural or non-natural amino acid of formula  $NH_2-CH(R^1)-COOH$ .

Examples of side chains of natural alpha amino acids include those of alanine, arginine, asparagine, aspartic acid, cysteine, cystine, glutamic acid, histidine, 5-hydroxylysine, 4-hydroxyproline, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine,  $\alpha$ -aminoadipic acid,  $\alpha$ -amino-n-butyric acid, 3,4-dihydroxyphenylalanine, homoserine,  $\alpha$ -methylserine, ornithine, pipecolic acid, and thyroxine.

Natural alpha-amino acids which contain functional substituents, for example amino, carboxyl, hydroxy, mercapto, guanidyl, imidazolyl, or indolyl groups in their characteristic side chains include arginine, lysine, glutamic acid, aspartic acid, tryptophan, histidine, serine, threonine, tyrosine, and cysteine. When  $R_3$  in the compounds of the invention is one of those side chains, the functional substituent may optionally be protected.

The term "protected" when used in relation to a functional substituent in a side chain of a natural alpha-amino acid means a derivative of such a substituent which is substantially non-functional. For example, carboxyl groups may be esterified (for example as a  $C_1-C_6$  alkyl ester), amino groups may be converted to amides (for example as a  $NHCOC_1-C_6$  alkyl amide) or carbamates (for example as an

NHC(=O)OC<sub>1</sub>-C<sub>6</sub> alkyl or NHC(=O)OCH<sub>2</sub>Ph carbamate), hydroxyl groups may be converted to ethers (for example an OC<sub>1</sub>-C<sub>6</sub> alkyl or a O(C<sub>1</sub>-C<sub>6</sub> alkyl)phenyl ether) or esters (for example a OC(=O)C<sub>1</sub>-C<sub>6</sub> alkyl ester) and thiol groups may be converted to thioethers (for example a tert-butyl or benzyl thioether) or thioesters (for example a SC(=O)C<sub>1</sub>-C<sub>6</sub> alkyl thioester).

Examples of side chains of non-natural alpha amino acids include those referred to below in the discussion of suitable R<sub>3</sub> groups for use in compounds of the present invention.

Salts of the compounds of the invention include physiologically acceptable acid addition salts for example hydrochlorides, hydrobromides, sulphates, methane sulphonates, p-toluenesulphonates, phosphates, acetates, citrates, succinates, lactates, tartrates, fumarates and maleates. Salts may also be formed with bases, for example sodium, potassium, magnesium, and calcium salts.

There are several chiral centres in the compounds according to the invention because of the presence of asymmetric carbon atoms. The presence of several asymmetric carbon atoms gives rise to a number of diastereomers with R or S stereochemistry at each chiral centre. All such diastereomers and mixtures thereof are included within the scope of the invention.

As previously stated, the compounds with which the present invention is concerned are principally distinguished from the compounds disclosed in the prior patent publications listed above by the ester or thioester group R<sub>4</sub>. Accordingly the groups R, R<sub>1</sub>, R<sub>2</sub>, and R<sub>3</sub>, may include those which have been disclosed in the corresponding positions of compounds disclosed in any of those prior art patent publications listed above. Without limiting the generality of the foregoing, examples of substituents R, to R<sub>4</sub> are given below:

The group R<sub>1</sub>

R<sub>1</sub> may be, for example,

hydrogen, methyl, ethyl, n-propyl, n-butyl, isobutyl, allyl, phenylpropyl, cyclopropylmethyl, phenylprop-2-enyl, thienylsulphanylmethyl, thienylsulphinylmethyl, or thienylsulphonylmethyl; or

C<sub>1</sub>-C<sub>4</sub> alkyl, eg methyl, ethyl n-propyl or n-butyl, substituted by a phthalimido, 1,2-dimethyl-3,5-dioxo-1,2,4-triazolidin-4-yl, 3-methyl-2,5-dioxo-1-imidazolidinyl, 3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl, 2-methyl-3,5-dioxo-1,2,4-oxadiazol-4-yl, 3-methyl-2,4,5-trioxo-1-imidazolidinyl, 2,5-dioxo-3-phenyl-1-imidazolidinyl, 2-oxo-1-pyrrolidinyl, 2,5-dioxo-1-pyrrolidinyl or 2,6-dioxopiperidinyl, 5,5-dimethyl-2,4-dioxo-3-oxazolidinyl, hexahydro-1,3-dioxopyrazolo[1.2,a][1.2,4]-triazol-2-yl, or a naphththalimido (ie 1,3-dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl), 1,3-dihydro-1-oxo-2H-benz[f]isoindol-2-yl, 1,3-dihydro-1,3-dioxo-2H-pyrrolo[3,4-b]quinolin-2-yl, or 2,3-dihydro-1,3-dioxo-1H-benz[d,e]isoquinolin-2-yl group; or

cyclohexyl, cyclooctyl, cycloheptyl, cyclopentyl, cyclobutyl, cyclopropyl, tetrahydropyranyl or morpholinyl.

Presently preferred R<sub>1</sub> groups include hydrogen, cyclopropylmethyl, n-propyl, and allyl.

The group R<sub>2</sub>

R<sub>2</sub> may for example be

C<sub>1</sub>-C<sub>12</sub> alkyl, C<sub>3</sub>-C<sub>8</sub> alkenyl or C<sub>3</sub>-C<sub>6</sub> alkynyl;

cycloalkyl(C<sub>1</sub>-C<sub>8</sub> alkyl)-;

phenyl(C<sub>1</sub>-C<sub>6</sub> alkyl)-, phenyl(C<sub>3</sub>-C<sub>8</sub> alkenyl)- or phenyl(C<sub>3</sub>-C<sub>6</sub> alkynyl)- optionally substituted in the phenyl ring;

heteroaryl(C<sub>1</sub>-C<sub>8</sub> alkyl)-, heteroaryl(C<sub>3</sub>-C<sub>8</sub> alkenyl)- or heteroaryl(C<sub>3</sub>-C<sub>8</sub> alkynyl)- optionally substituted in the heteroaryl ring;

4-phenylphenyl(C<sub>1</sub>-C<sub>8</sub> alkyl)-, 4-phenylphenyl(C<sub>3</sub>-C<sub>8</sub> alkenyl)-, 4-phenylphenyl(C<sub>3</sub>-C<sub>8</sub> alkynyl)-, 4-heteroarylphenyl(C<sub>1</sub>-C<sub>8</sub> alkyl)-, 4-heteroarylphenyl(C<sub>3</sub>-C<sub>8</sub> alkenyl)-, 4-heteroarylphenyl(C<sub>3</sub>-C<sub>8</sub> alkynyl)-, optionally substituted in the terminal phenyl or heteroaryl ring;

phenoxy(C<sub>1</sub>-C<sub>8</sub> alkyl)- or heteroaryloxy(C<sub>1</sub>-C<sub>8</sub> alkyl)- optionally substituted in the phenyl or heteroaryl ring;

Specific examples of such groups include methyl, ethyl, n- or iso-propyl, n-, iso- or tert-butyl, n-pentyl, n-hexyl, n-heptyl, n-nonyl, n-decyl, prop-2-yn-1-yl, cyclohexylethyl, cyclopentylmethyl, 3-phenylprop-2-yn-1-yl, 3-(2-chlorophenyl)prop-2-yn-1-yl, benzyl phenylpropyl, 4-chlorophenylpropyl, 4-methylphenylpropyl, 4-methoxyphenylpropyl, phenoxybutyl, 3-(4-pyridylphenyl)propyl-, 3-(4-(4-pyridyl)phenyl)prop-2-yn-1-yl, 3-(4-phenylphenyl)propyl-, 3-(4-phenyl)phenyl)prop-2-yn-1-yl and 3-[(4-chlorophenyl)phenyl]propyl-.

Presently preferred R<sub>2</sub> groups include benzyl, n-butyl, iso-butyl, n-hexyl, and cyclopentylmethyl

#### The group R<sub>3</sub>

R<sub>3</sub> may for example be C<sub>1</sub>-C<sub>8</sub> alkyl, phenyl, 2-, 3-, or 4-pyridyl, 2- or 3-thienyl, 2-, 3-, or 4-hydroxyphenyl, 2-, 3-, or 4-methoxyphenyl, 2-, 3-, or 4-pyridylmethyl, benzyl, 2-, 3-, or 4-hydroxybenzyl, 2-, 3-, or 4-benzyloxybenzyl, 2-, 3-, or 4-C<sub>1</sub>-C<sub>8</sub> alkoxybenzyl, or benzyloxy(C<sub>1</sub>-C<sub>8</sub>alkyl)-; or

the characterising group of a natural α-amino acid, in which any functional group may be protected, any amino group may be acylated and any carboxyl

group present may be amidated; or

a group  $-[\text{Alk}]_n\text{R}_6$  where Alk is a  $(\text{C}_1-\text{C}_6)$ alkyl or  $(\text{C}_2-\text{C}_6)$ alkenyl group optionally interrupted by one or more -O-, or -S- atoms or  $-\text{N}(\text{R}_7)-$  groups [where  $\text{R}_7$  is a hydrogen atom or a  $(\text{C}_1-\text{C}_6)$ alkyl group], n is 0 or 1, and  $\text{R}_6$  is an optionally substituted cycloalkyl or cycloalkenyl group; or

a benzyl group substituted in the phenyl ring by a group of formula -  
 $\text{OCH}_2\text{COR}_8$  where  $\text{R}_8$  is hydroxyl, amino,  $(\text{C}_1-\text{C}_6)$ alkoxy, phenyl $(\text{C}_1-\text{C}_6)$ alkoxy,  
 $(\text{C}_1-\text{C}_6)$ alkylamino, di $(\text{C}_1-\text{C}_6)$ alkylamino, phenyl $(\text{C}_1-\text{C}_6)$ alkylamino, the residue  
of an amino acid or acid halide, ester or amide derivative thereof, said residue  
being linked via an amide bond, said amino acid being selected from glycine,  
 $\alpha$  or  $\beta$  alanine, valine, leucine, isoleucine, phenylalanine, tyrosine, tryptophan,  
serine, threonine, cysteine, methionine, asparagine, glutamine, lysine,  
histidine, arginine, glutamic acid, and aspartic acid; or

a heterocyclic $(\text{C}_1-\text{C}_6)$ alkyl group, either being unsubstituted or mono- or di-  
substituted in the heterocyclic ring with halo, nitro, carboxy,  $(\text{C}_1-\text{C}_6)$ alkoxy,  
cyano,  $(\text{C}_1-\text{C}_6)$ alkanoyl, trifluoromethyl  $(\text{C}_1-\text{C}_6)$ alkyl, hydroxy, formyl, amino,  
 $(\text{C}_1-\text{C}_6)$ alkylamino, di $(\text{C}_1-\text{C}_6)$ alkylamino, mercapto,  $(\text{C}_1-\text{C}_6)$ alkylthio,  
hydroxy $(\text{C}_1-\text{C}_6)$ alkyl, mercapto $(\text{C}_1-\text{C}_6)$ alkyl or  $(\text{C}_1-\text{C}_6)$ alkylphenylmethyl; or

a group  $-\text{CR}_a\text{R}_b\text{R}_c$  in which:

each of  $\text{R}_a$ ,  $\text{R}_b$  and  $\text{R}_c$  is independently hydrogen,  $(\text{C}_1-\text{C}_6)$ alkyl,  $(\text{C}_2-\text{C}_6)$ alkenyl,  $(\text{C}_2-\text{C}_6)$ alkynyl, phenyl $(\text{C}_1-\text{C}_6)$ alkyl,  $(\text{C}_3-\text{C}_8)$ cycloalkyl; or

$\text{R}_c$  is hydrogen and  $\text{R}_a$  and  $\text{R}_b$  are independently phenyl or heteroaryl such as pyridyl; or

$\text{R}_c$  is hydrogen,  $(\text{C}_1-\text{C}_6)$ alkyl,  $(\text{C}_2-\text{C}_6)$ alkenyl,  $(\text{C}_2-\text{C}_6)$ alkynyl, phenyl $(\text{C}_1-$



$C_6$ )alkyl, or  $(C_3-C_8)$ cycloalkyl, and  $R_a$  and  $R_b$  together with the carbon atom to which they are attached form a 3 to 8 membered cycloalkyl or a 5- to 6-membered heterocyclic ring; or

$R_s$ ,  $R_b$  and  $R_c$  together with the carbon atom to which they are attached form a tricyclic ring (for example adamantyl); or

$R_a$  and  $R_b$  are each independently  $(C_1-C_8)$ alkyl,  $(C_2-C_8)$ alkenyl,  $(C_2-C_8)$ alkynyl, phenyl $(C_1-C_8)$ alkyl, or a group as defined for  $R_c$  below other than hydrogen, or  $R_a$  and  $R_b$  together with the carbon atom to which they are attached form a cycloalkyl or heterocyclic ring, and  $R_c$  is hydrogen, -OH, -SH, halogen, -CN, -CO<sub>2</sub>H,  $(C_1-C_4)$ perfluoroalkyl, -CH<sub>2</sub>OH, -CO<sub>2</sub> $(C_1-C_8)$ alkyl, -O $(C_1-C_8)$ alkyl, -O $(C_2-C_8)$ alkenyl, -S $(C_1-C_8)$ alkyl, -SO $(C_1-C_8)$ alkyl, -SO<sub>2</sub> $(C_1-C_8)$ alkyl, -S $(C_2-C_8)$ alkenyl, -SO $(C_2-C_8)$ alkenyl, -SO<sub>2</sub> $(C_2-C_8)$ alkenyl or a group -Q-W wherein Q represents a bond or -O-, -S-, -SO- or -SO<sub>2</sub>- and W represents a phenyl, phenylalkyl,  $(C_3-C_8)$ cycloalkyl,  $(C_3-C_8)$ cycloalkylalkyl,  $(C_4-C_8)$ cycloalkenyl,  $(C_4-C_8)$ cycloalkenylalkyl, heteroaryl or heteroarylalkyl group, which group W may optionally be substituted by one or more substituents independently selected from, hydroxyl, halogen, -CN, -CO<sub>2</sub>H, -CO<sub>2</sub> $(C_1-C_8)$ alkyl, -CONH<sub>2</sub>, -CONH $(C_1-C_8)$ alkyl, -CONH $(C_1-C_8)$ alkyl)<sub>2</sub>, -CHO, -CH<sub>2</sub>OH,  $(C_1-C_4)$ perfluoroalkyl, -O $(C_1-C_8)$ alkyl, -S $(C_1-C_8)$ alkyl, -SO $(C_1-C_8)$ alkyl, -SO<sub>2</sub> $(C_1-C_8)$ alkyl, -NO<sub>2</sub>, -NH<sub>2</sub>, -NH $(C_1-C_8)$ alkyl, -N $(C_1-C_8)$ alkyl)<sub>2</sub>, -NHCO $(C_1-C_8)$ alkyl,  $(C_1-C_8)$ alkyl,  $(C_2-C_8)$ alkenyl,  $(C_2-C_8)$ alkynyl,  $(C_3-C_8)$ cycloalkyl,  $(C_4-C_8)$ cycloalkenyl, phenyl or benzyl.

Examples of particular  $R_3$  groups include benzyl, phenyl, cyclohexylmethyl, pyridin-3-ylmethyl, tert-butoxymethyl, iso-propyl, iso-butyl, sec-butyl, tert-butyl, 1-benzylthio-1-methylethyl, 1-methylthio-1-methylethyl, and 1-mercapto-1-methylethyl.

Presently preferred  $R_3$  groups include phenyl, benzyl, tert-butoxymethyl, iso-propyl

and iso-butyl.

The group  $R_4$

Examples of particular ester and thioester groups  $R_4$  groups include those of formula  $-(C=O)OR_9$ ,  $-(C=O)SR_9$ ,  $-(C=S)SR_9$ , and  $-(C=S)OR_9$  wherein  $R_9$  is  $(C_1-C_8)$ alkyl,  $(C_2-C_8)$ alkenyl, cycloalkyl, cycloalkyl $(C_1-C_8)$ alkyl-, phenyl, heterocyclyl, phenyl $(C_1-C_8)$ alkyl-, heterocyclyl $(C_1-C_8)$ alkyl-,  $(C_1-C_8)$ alkoxy $(C_1-C_8)$ alkyl-,  $(C_1-C_8)$ alkoxy $(C_1-C_8)$ alkoxy $(C_1-C_8)$ alkyl-, any of which may be substituted on a ring or non-ring carbon atom or on a ring heteroatom, if present. Examples of such  $R_9$  groups include methyl, ethyl, n- and iso-propyl, n-, sec- and tert-butyl, 1-ethyl-prop-1-yl, 1-methyl-prop-1-yl, 1-methyl-but-1-yl, cyclopentyl, cyclohexyl, allyl, phenyl, benzyl, 2-, 3- and 4-pyridylmethyl, N-methylpiperidin-4-yl, 1-methylcyclopent-1-yl, adamantyl, tetrahydrofuran-3-yl and methoxyethyl.

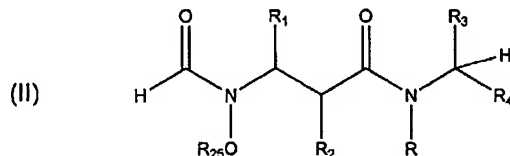
Presently preferred are compounds of formula (IB) wherein  $R_4$  is a carboxylate ester of formula  $-(C=O)OR_9$ , wherein  $R_9$  is benzyl, cyclopentyl, cyclohexyl, or isopropyl.

The group R

Presently preferred R groups are hydrogen and methyl.

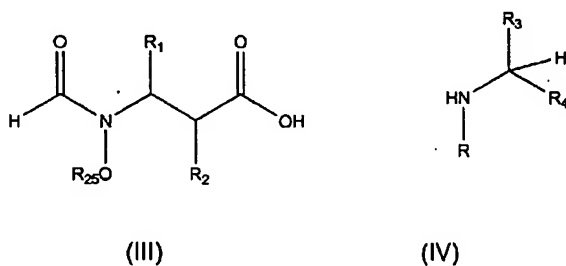
Specific examples of compounds of the invention include those prepared according to the Examples below, and salts, hydrates and solvates thereof.

Compounds of the invention may be prepared by deprotecting an O-protected N-formyl-N-hydroxyamino compound of formula (II):



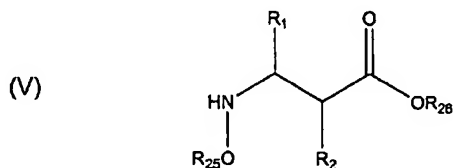
in which  $R_1$ ,  $R_2$ ,  $R_3$  and  $R_4$  are as defined in general formula (I) and  $R_{25}$  is a hydroxy protecting group removable to leave a hydroxy group by hydrogenolysis or hydrolysis. Benzyl is a preferred  $R_{25}$  group for removal by hydrogenolysis, and tetrahydropyranyl is a preferred group for removal by acid hydrolysis.

Compounds of formula (II) may be prepared by causing an acid of formula (III) or an activated derivative thereof to react with an amine of formula (IV)



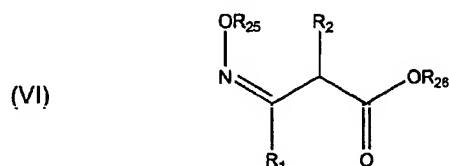
wherein  $R_1$ ,  $R_2$ ,  $R_3$  and  $R_4$  are as defined in general formula (I) except that any substituents in  $R_1$ ,  $R_2$ ,  $R_3$  and  $R_4$  which are potentially reactive in the coupling reaction may themselves be protected from such reaction, and  $R_{25}$  is as defined in relation to formula (II) above, and optionally removing protecting groups from  $R_1$ ,  $R_2$ ,  $R_3$  and  $R_4$ .

Compounds of formula (III) may be prepared by N-formylation, for example using acetic anhydride and formic acid, of compounds of formula (V)



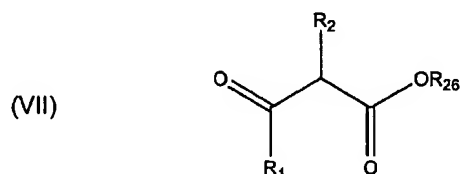
wherein  $R_1$ ,  $R_2$  and  $R_{25}$  are as defined in relation to formula (II) and  $R_{26}$  is a hydroxy protecting group, and thereafter removing the protecting group  $R_{26}$ .

A compound of general formula (V) may be prepared by reduction of an oxime of general formula (VI)



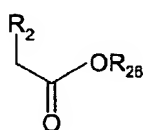
wherein  $R_1$ ,  $R_2$ ,  $R_{25}$  and  $R_{26}$  are as defined above. Reducing agents include metal hydrides (eg sodium cyanoborohydride in acetic acid, triethylsilane or borane/pyridine) and hydrogenation.

A compound of general formula (VI) can be prepared by reaction of a  $\beta$ -keto carbonyl compound of general formula (VII)

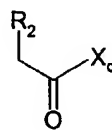


wherein  $R_1$ ,  $R_2$ , and  $R_{26}$  are as defined above, with an O-protected hydroxylamine.

$\beta$ -keto carbonyl compounds (VI) may be prepared by acylation of the enolate derived from a carbonyl compound of formula (VII) or (VIIA)



(VII)



(VIIA)

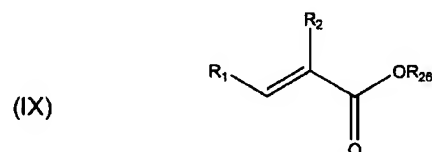
wherein  $R_2$  and  $R_{26}$  are as defined above, and  $X_c$  is a chiral auxiliary, with a compound of formula (VII)

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wherein R<sub>1</sub> is as defined above and Z is a leaving group such as chloro or alkoxy. Chiral enolates of type (VIIA) have been described by Evans (J. Am. Chem. Soc., 104, 1737, (1982)).

Another method for the preparation of a compound of general formula (IV) is by Michael addition of a hydroxylamine derivative to an  $\alpha$ ,  $\beta$ -unsaturated carbonyl compounds of general formula (IX)



wherein R<sub>1</sub>, R<sub>2</sub>, and R<sub>28</sub> are as defined above. The  $\alpha$ ,  $\beta$ -unsaturated carbonyl compounds (IX) may be prepared by standard methods.

The compounds with which the invention is concerned may be prepared for administration by any route consistent with their pharmacokinetic properties.

Orally administrable compositions may be in the form of tablets, capsules, powders, granules, lozenges, liquid or gel preparations, such as oral, topical, or sterile parenteral solutions or suspensions. Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinyl-pyrrolidone; fillers for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tableting lubricant, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants for example potato starch, or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be

5 coated according to methods well known in normal pharmaceutical practice. Oral  
liquid preparations may be in the form of, for example, aqueous or oily suspensions,  
10 solutions, emulsions, syrups or elixirs, or may be presented as a dry product for  
reconstitution with water or other suitable vehicle before use. Such liquid  
preparations may contain conventional additives such as suspending agents, for  
15 example sorbitol, syrup, methyl cellulose, glucose syrup, gelatin hydrogenated  
edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia;  
non-aqueous vehicles (which may include edible oils), for example almond oil,  
fractionated coconut oil, oily esters such as glycerine, propylene glycol, or ethyl  
20 alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic  
acid, and if desired conventional flavouring or colouring agents.

25 For topical application to the skin, the drug may be made up into a cream, lotion or  
ointment. Cream or ointment formulations which may be used for the drug are  
conventional formulations well known in the art, for example as described in  
standard textbooks of pharmaceuticals such as the British Pharmacopoeia.

30 The active ingredient may also be administered parenterally in a sterile medium.  
Depending on the vehicle and concentration used, the drug can either be suspended  
35 or dissolved in the vehicle. Advantageously, adjuvants such as a local anaesthetic,  
preservative and buffering agents can be dissolved in the vehicle.

40 It will be understood that the specific dose level for any particular patient will depend  
upon a variety of factors including the activity of the specific compound employed,  
the age, body weight, general health, sex, diet, time of administration, route of  
administration, rate of excretion, drug combination and the severity of the particular  
45 disease undergoing therapy.

The following preparative Examples describe the preparation of compounds useful in  
50 accordance with the invention

The following abbreviations have been used in the examples

DCM - Dichloromethane

DMF - N,N-Dimethylformamide

HOBT - 1-Hydroxybenzotriazole

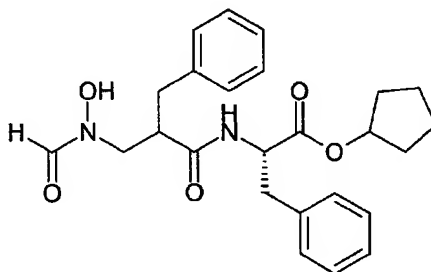
WSCDI - N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride

HCl - Hydrochloric acid

THF - Tetrahydrofuran

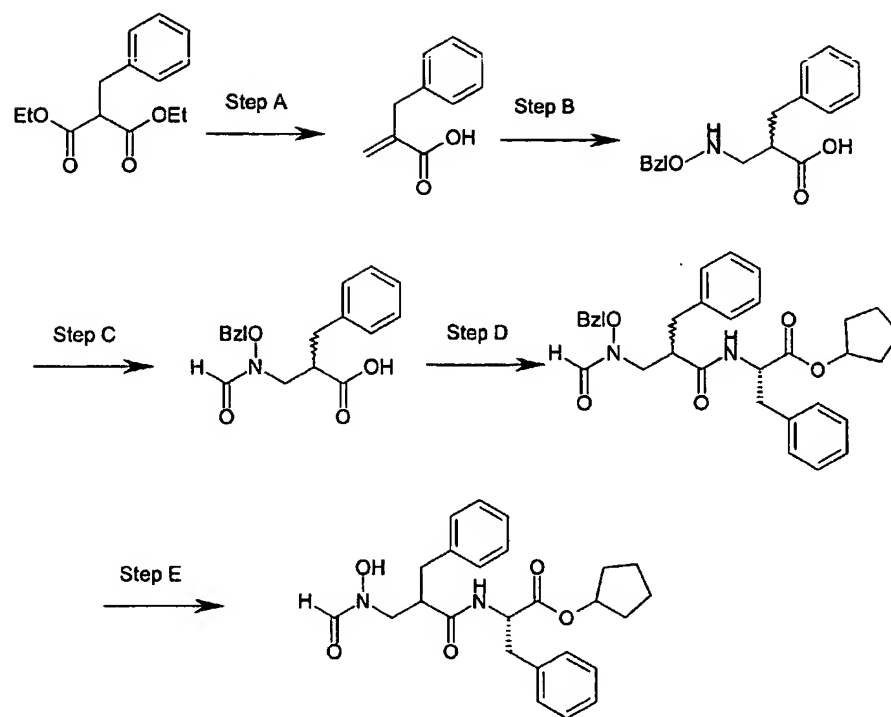
#### Example 1

2S-[2-(R,S)-Benzyl-3-(formyl-hydroxy-amino)-propionylamino]-3-phenyl-propionic acid cyclopentyl ester



Example 1 was prepared as outlined in Scheme 1 using procedures described below.

Scheme 1



Reagents and conditions: A. (1) EtOH/KOH/H<sub>2</sub>O, reflux 5 hours, (2) piperidine, HCHO, EtOH, reflux 4 hours; B. H<sub>2</sub>NOBzl, 80°C o/n; C. HCOOH, Ac<sub>2</sub>O; D. WSCDI, HOBT, DMF, L-phenylalanine cyclopentyl ester r.t., 18 hours; E. H<sub>2</sub>(g), Pd catalyst, EtOH 90 minutes.



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## (a) 2-Benzyl-acrylic acid

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Diethyl benzylmalonate (100g, 400mmol) was dissolved in ethanol (300mL) and treated with a solution of potassium hydroxide (134.4g, 2.4mol) in water (500mL). The mixture was heated under reflux for 5 hours and then allowed to cool. Ethanol was removed under reduced pressure and the remaining aqueous solution cooled in ice and acidified to pH1 with concentrated HCl. The product was extracted with ethyl acetate (3x200mL). The combined extracts were washed with brine, dried over magnesium sulphate, filtered and concentrated under reduced pressure to yield benzylmalonic acid as a white crystalline solid. The solid was taken-up in ethanol (250mL) and treated portionwise with piperidine (33g, 397mmol) followed by an aqueous solution of formaldehyde (37%, 150mL) which resulted in formation of a white precipitate. The reaction mixture was heated and treated with methanol (50mL) to give a homogeneous solution. Following dissolution the reaction mixture was heated under reflux for 4 hours. The reaction mixture was concentrated under reduced pressure. The aqueous residue was acidified to pH1 with 1M HCl and the product extracted with ethyl acetate (3x150mL). The combined extracts were washed with brine, dried over magnesium sulphate, filtered and concentrated under reduced pressure to yield 2-benzyl-acrylic acid as a colourless oil which crystallized on standing (45g, 75%). <sup>1</sup>H-NMR;  $\delta$  (CDCl<sub>3</sub>), 7.32-7.17 (5H, m), 6.36 (1H, s), 5.54 (1H, d, J=1.3Hz), 3.61 (2H, s).

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## (b) 2-(R,S)-Benzyl-3-benzyloxyamino-propionic acid

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A mixture of 2-benzyl-acrylic acid (8.0g, 55mmol) and O-benzylhydroxylamine (16.0g, 130mmol) was heated at 80°C for 18 hours. The reaction mixture was cooled, diluted with diethyl ether (100mL) and extracted with 1M sodium carbonate (3x100mL). The combined aqueous extracts were acidified with 3M citric acid and then re-extracted with DCM (3x100mL). The combined organic extracts were washed with brine, dried over magnesium sulphate, filtered and concentrated under reduced pressure to yield 2-(R,S)-benzyl-3-benzyloxyamino-propionic acid as a

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white crystalline solid (7.82g, 53%). <sup>1</sup>H-NMR; δ (CDCl<sub>3</sub>), 7.61-7.15 (10H, m), 4.66 (2H, d, J=1.7Hz), 3.13-2.94 (4H, m), 2.84-2.74 (1H, m).

(c) 2-(R,S)-Benzyl-3-(benzyloxy-formyl-amino)-propionic acid

A solution of 2-(R,S)-benzyl-3-benzyloxyamino-propionic acid (7.8g, 27.4mmol) in formic acid (40mL) was cooled in an ice-water bath and treated dropwise with acetic anhydride (15mL). The reaction was allowed to warm to room temperature and stirred for 18 hours. The reaction mixture was diluted with DCM (150mL) and partitioned with water (100mL). The organic layer was separated, washed with brine, dried over magnesium sulphate, filtered and concentrated under reduced pressure to yield 2-(R,S)-benzyl-3-(benzyloxy-formyl-amino)-propionic acid as a colourless oil (7.8g, 91%). <sup>1</sup>H-NMR; δ (CDCl<sub>3</sub>), 7.87-7.16 (10H, m), 4.92-4.66 (2H, m), 4.03-3.90 (2H, m), 3.17-2.93 (2H, m), 2.78-2.70 (1H, m).

(d) 2S-[2-(R,S)-Benzyl-3-(benzyloxy-formyl-amino)-propionylamino]-3-phenyl propionic acid cyclopentyl ester

2-(R,S)-Benzyl-3-(benzyloxy-formyl-amino)-propionic acid (2.89g, 9.3mmol) was dissolved in DMF (20mL) and treated with HOBT (1.35g, 10mmol) and WSCDI (1.91g, 10mmol). The reaction mixture was stirred at room temperature for 1 hour before the addition of a solution of L-phenylalanine cyclopentyl ester (2.4g, 10.3mmol) in DMF (10mL). The reaction mixture was stirred at room temperature for 18 hours. DMF was removed under reduced pressure and the residue partitioned between ethyl acetate and 1M HCl. The organic layer was separated and washed with 1M HCl, saturated aqueous sodium bicarbonate solution and brine before drying over magnesium sulphate, filtration and concentration under reduced pressure to yield 2S-[2-(R,S)-benzyl-3-(benzyloxy-formyl-amino)-propionylamino]-3-phenylpropionic acid cyclopentyl ester (3.6g used crude in step e).

(e) 2S-[2-(R,S)-Benzyl-3-(formyl-hydroxy-amino)-propionylamino]-3-phenyl-propionic

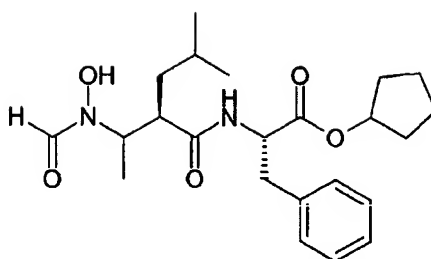
acid cyclopentyl ester

A solution of 2S-[2-(R,S)-benzyl-3-(benzyloxy-formyl-amino)-propionylamino]-3-phenyl propionic acid cyclopentyl ester (3.6g crude from step d) in ethanol (30mL) was treated with a palladium catalyst (100mg, 10%Pd on charcoal). The reaction mixture was stirred under an atmosphere of hydrogen gas for 90 minutes. Catalyst was removed by filtration and the filtrate concentrated to a colourless oil. Using reverse phase chromatography 200mg of the crude product was fractionated to provide two diastereoisomers of 2S-[2-benzyl-3-(formyl-hydroxy-amino)-propionylamino]-3-phenyl-propionic acid cyclopentyl ester. Diastereoisomer A (35mg),  $^1\text{H-NMR}$ ;  $\delta$  ( $\text{CDCl}_3$ ), 8.34 and 7.77 (1H, 2xs), 7.29-6.84 (10H, m), 6.13 (1H, d,  $J=7.3\text{Hz}$ ), 5.11-5.00 (1H, m), 4.67-4.49 (1H, m), 3.99-3.79 (1H, m), 3.66-3.60 and 3.51-3.47 (1H, 2xm), 3.05-2.69 (5H, m) and 1.85-1.45 (8H, m);  $^{13}\text{C-NMR}$ ;  $\delta$ ( $\text{CDCl}_3$ ), 174.4, 172.3, 171.4, 171.2, 138.2, 136.3, 129.8, 129.6, 129.2, 128.9, 127.5, 127.4, 127.2, 79.4, 78.9, 54.3, 54.0, 51.9, 51.1, 48.8, 47.9, 46.6, 38.7, 38.1, 36.8, 36.5, 33.0, 32.8 and 24.0. Diastereoisomer B (42mg),  $^1\text{H-NMR}$ ;  $\delta$  ( $\text{CDCl}_3$ ), 8.35 and 7.71 (1H, 2xs), 7.33-7.15 (8H, m), 7.08-6.94 (1H, bm), 6.83-6.73 (2H, m), 6.20 and 5.94 (2xd), 5.30-5.08 (1H, m), 4.73-4.64 (1H, m), 3.85-3.76 (1H, m), 3.56-3.47 (1H, m), 3.01-2.68 (5H, m) and 1.91-1.45 (8H, m);  $^{13}\text{C-NMR}$ ;  $\delta$ ( $\text{CDCl}_3$ ), 174.2, 172.9, 172.4, 171.8, 138.7, 136.1, 129.6, 129.3, 129.1, 128.9, 128.8, 127.6, 127.5, 127.4, 127.3, 127.2, 127.1, 79.9, 79.2, 53.9, 53.6, 52.3, 50.3, 48.1, 47.0, 38.3, 37.5, 36.9, 36.4, 32.9, 32.8 and 24.0.

## Example 2

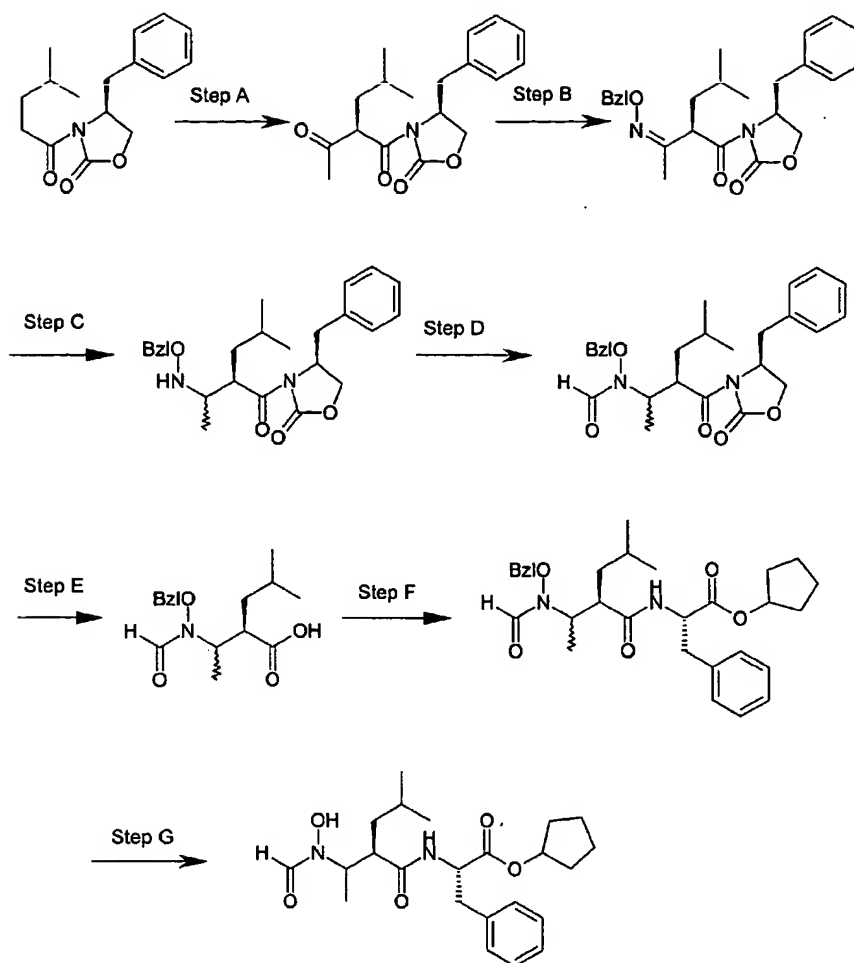
2S-{2R-[1-(R,S)-(Formyl-hydroxy-amino)-ethyl]-4-methyl-pentanoylamino}-3-phenylpropionic acid cyclopentyl ester

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Example 2 was prepared as outlined in scheme 2 using procedures described below.

## Scheme 2



Reagents and conditions: A. Sodium hexamethyldisilazide, AcCl, -60°C 3 hours; B. BzIOH<sub>2</sub> HCl, NaOAc, H<sub>2</sub>O/EtOH, 50°C 18 hours; C. AcOH, NaCNBH<sub>3</sub>, 25 hours; D. HCOOH, AcOH, 18 hours; E. LiOH, H<sub>2</sub>O<sub>2</sub>, THF/H<sub>2</sub>O, 4 hours; F. L-Phenylalanine cyclopentyl ester, HOBt, WSCDI, DMF, 48 hours; G. H<sub>2</sub>(g), Pd catalyst, EtOH, 2 hours.

(a) 1-(4S-Benzyl-2-oxo-oxazolidin-3-yl)-2R-isobutyl-butane-1,3-dione

A solution of 4S-benzyl-3-(4-methyl-pentanoyl)-oxazolidin-2-one (31g, 113mmol) in anhydrous THF (750mL) was cooled to -70°C under an inert atmosphere. Sodium hexamethyldisilazide (118mL of a 1M solution, 118mmol) was added via cannula whilst maintaining the temperature below -68°C. The reaction mixture was stirred at -70°C for 30 minutes before the addition of acetyl chloride (10.2mL, 135mmol), again maintaining the temperature below -68°C. The reaction was slowly warmed to -60°C and maintained at this temperature for 3 hours before quenching with acetic acid (6.75g, 118mmol) in diethyl ether (10mL). The solvent was removed under reduced pressure and the resulting slurry taken up in ethyl acetate and washed with brine. The organic layer was dried over sodium sulphate, filtered and concentrated under reduced pressure to leave an oil (36g) which was shown by NMR to contain the title compound contaminated with 15% of the starting material. <sup>1</sup>H-NMR; δ (CDCl<sub>3</sub>), 7.35-7.22 (5H, m), 4.69-4.65 (1H, m), 4.63-4.57 (1H, dd, J=3.2Hz), 4.22-4.13 (2H, m), 3.41 (1H, dd, J=3.2Hz), 2.74 (1H, dd, J=9.8Hz), 2.31 (3H, s), 2.10-2.04 (1H, m), 1.68-1.60 (1H, m), 1.49-1.39 (1H, m) and 0.97 (6H, 2xd, J=6.5Hz).

(b) 1-(4S-Benzyl-2-oxo-oxazolidin-3-yl)-2R-isobutyl-butane 1,3-dione 3-(O-benzyl-oxime)

1-(4S-Benzyl-2-oxo-oxazolidin-3-yl)-2R-isobutyl-butane-1,3-dione (35.5g, 112mmol) was dissolved in water/ethanol (500mL, 10%vol/vol) and treated with benzylhydroxylamine hydrochloride (21.4g, 134mmol) and sodium acetate (18.3g, 134mmol). The reaction mixture was stirred at 50°C for 18 hours. The solution was concentrated under reduced pressure to give a white precipitate of the product which was collected by filtration (21.0g, 44%). <sup>1</sup>H-NMR; δ (CDCl<sub>3</sub>), 7.38-7.08 (10H, m), 5.15-5.04 (2H, m), 4.57-4.47 (1H, m), 4.24 (1H, dd, J=3.6Hz), 4.07 (1H, dd, J=8.9Hz), 3.92 (1H, dd, J=2.6Hz), 3.16 (1H, dd, J=2.7Hz), 2.09 (3H, s), 2.04-1.98 (1H, m), 1.76-1.66 (1H, dd, J=11.0Hz), 1.63-1.60 (1H, m), 1.45-1.35 (1H, m) and 0.94 (6H, 2xd, J=6.6Hz).

(c) 4S-Benzyl-3-[2R-(1-(R,S)-benzyloxyamino-ethyl)-4-methyl-pentanoyl]-oxazolidin-2-one

1-(4S-Benzyl-2-oxo-oxazolidin-3-yl)-2R-isobutyl-butane 1,3-dione 3-(O-benzyl-oxime) (21g, 50mmol) was dissolved in acetic acid (400mL) and sodium cyanoborohydride (6.24g, 100mmol) added portionwise. The mixture was stirred for 18 hours at room temperature then a further equivalent of sodium cyanoborohydride added. Stirring was continued for a further 7 hours then the reaction mixture concentrated under reduced pressure. The resultant oil was taken up in DCM (600mL) then carefully washed with sodium carbonate and brine. The organic layer was dried over magnesium sulphate, filtered and evaporated to a colourless oil (21g). Column chromatography on silica gel using DCM as eluent lead to isolation of the desired product as a mixture of diastereoisomers (9.05g, 43%). <sup>1</sup>H-NMR; δ (CDCl<sub>3</sub>), 7.37-7.18 (10H, m), 5.80 (1H, bs), 4.70-4.60 (3H, m), 4.13 (1H, m), 4.12-4.05 (2H, m), 3.91 (1H, m), 3.43-3.36 (1H, m), 2.48-2.37 (1H, m), 2.00-1.75 (1H, m), 1.70-1.64 (1H, m), 1.40-1.31 (1H, m), 1.24 (3H, m) and 0.94-0.87 (6H, m).

(d) N-[2-(4S-Benzyl-2-oxo-oxazolidine-3S-carbonyl)-1-(R,S),4-dimethyl-pentyl]-N-benzyloxyformamide

4S-Benzyl-3-[2R-(1-(R,S)-benzyloxyamino-ethyl)-4-methyl-pentanoyl]-oxazolidin-2-one (12.7g, 30mmol) was taken up in formic acid (250mL) and stirred at 0°C while acetic anhydride (50mL) was added dropwise. The mixture was stirred at room temperature for 18 hours. The reaction mixture was concentrated under reduced pressure, taken up in DCM and washed with saturated sodium bicarbonate and brine. The solution was dried over magnesium sulphate, filtered and concentrated to yield the title compound as a colourless oil (12.7g, 94%). <sup>1</sup>H-NMR; δ (CDCl<sub>3</sub>, mixture of diastereoisomers), 8.35 and 8.14 (1H, 2xbs), 7.55-7.15 (10H, m), 5.20-4.90 (2H, bm), 4.73-4.46 (2H, m), 4.20-4.01 (3H, m), 3.31 (1H, dt, J=13.2, 3.2Hz), 2.51-2.30 (1H, m), 1.95-1.74 (1H, bm), 1.54-1.33 (5H, bm), 0.98-0.85 (6H, m).

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(e) 2R-[1-(R,S)-(Benzyloxy-formyl-amino)-ethyl]-4-methyl-pentanoic acid

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N-[2-(4S-Benzyl-2-oxo-oxazolidine-3S-carbonyl)-1-(R,S),4-dimethyl-pentyl]-N-benzyloxyformamide (7.30g, 16.1mmol) was dissolved in THF (210mL) and water (60mL) and cooled to 0°C. Hydrogen peroxide (1.84mL, 30% solution, 64.5mmol) was added dropwise followed by aqueous lithium hydroxide (1.02g in 10mL, 15 24.2mmol) and the solution stirred at 0°C for 4 hours. The reaction mixture was quenched by the addition of sodium nitrite (1.11g, 16mmol). THF was removed under reduced pressure and the chiral auxilliary removed by extraction into DCM. The aqueous solution was neutralised (pH5) with 1M HCl and extracted with 20 ethyl acetate. The combined extracts were dried over magnesium sulphate, filtered and concentrated to yield the product as a yellow oil (3.78g, 80%). <sup>1</sup>H-NMR; δ (CDCl<sub>3</sub>, mixture of diastereoisomers), 8.40 and 8.00 (1H, 2xs), 7.52-7.26 (5H, m), 25 5.25-4.85 (2H, 2xbd), 4.45 (1H, m), 3.85 (1H, bm), 2.90 (1H, bm), 1.75-1.48 (2H, bm), 1.48-1.20 (4H, bm) and 1.00-0.84 (6H, m).

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(f) 2S-[2R-[1-(R,S)-(Benzyloxy-formyl-amino)-ethyl]-4-methyl-pentanoylamino]-3-phenyl-propionic acid cyclopentyl ester

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A solution of 2R-[1-(R,S)-(benzyloxy-formyl-amino)-ethyl]-4-methyl-pentanoic acid (410mg, 1.40mmol) in DMF (10mL) was treated with HOBT (227mg, 1.68mmol) and WSCDI (322mg, 1.68mmol). A solution of L-phenylalanine cyclopentyl ester (394mg, 1.68mmol) in DMF (2mL) was added to the reaction mixture. The reaction 40 was stirred at room temperature for 48 hours. DMF was removed by evaporation under reduced pressure. The residue was taken up in ethyl acetate and washed with 1M HCl, saturated sodium bicarbonate and brine, before drying over 45 magnesium sulphate, filtration and concentration to a colourless oil. The product was purified by column chromatography on silica gel eluting with 20-40% ethyl acetate/hexane. Product containing fractions were combined and solvent evaporated to provide the title compound as an off-white foam (571mg, 66%). <sup>1</sup>H-NMR; δ (CDCl<sub>3</sub>, mixture of diastereoisomers), 8.19 and 7.97 (1H, 2xs), 7.50-6.90 50

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(10H, m), 6.09 and 5.94 (1H, 2xbd), 5.34-5.02 (2H, m), 4.95-4.74 (2H, m), 3.91-3.61 (2H, 2xbm), 3.15-2.80 (2H, m), 2.80-2.60 and 2.55-2.35 (1H, 2xm), 1.92-1.35 (11H, m), 1.22-1.00 (2H, m), 0.95-0.82 (6H, m).

(g) 2S-{2R-[1-(R,S)-(Formyl-hydroxy-amino)-ethyl]-4-methyl-pentanoylamino}-3-phenylpropionic acid cyclopentyl ester

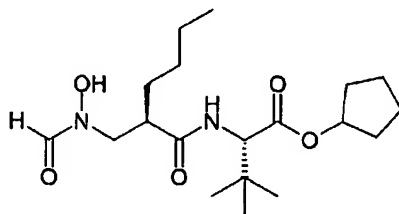
A solution of 2S-{2R-[1-(R,S)-(benzyloxy-formyl-amino)-ethyl]-4-methyl-pentanoyl amino}-3-phenyl-propionic acid cyclopentyl ester (447mg, 0.88mmol) in ethanol (25mL) was treated with palladium catalyst (89mg, 10% Pd on charcoal) as a slurry in ethyl acetate (2mL). Hydrogen gas was bubbled through the resulting suspension for 2 hours. The catalyst was removed by filtration and the filtrate concentrated under reduced pressure to a white foam. The reaction product was separated by preparative reverse phase chromatography to yield two diastereoisomers.

Diastereoisomer A (41mg, 11%), <sup>1</sup>H-NMR; δ (methanol-d<sub>4</sub>), 8.60 (0.6H, d, J=8.2Hz), 8.52 (0.4H, d, J=8.2Hz), 8.24 (0.4H, s), 7.90 (0.6H, s), 7.84-7.15 (5H, m), 5.15 (1H, m), 4.79-4.71 (1H, m), 4.34-4.22 (0.4H, m), 3.66-3.54 (0.7H, m), 3.25-3.15 (1H, m), 2.90 (1H, dd, J=14.0, 10.4Hz), 2.70-2.56 (1H, m), 1.87-1.40 (10H, bm), 1.13-0.97 (1H, m) and 0.91-0.75 (9H, bm); <sup>13</sup>C-NMR; δ(methanol-d<sub>4</sub>), 175.9, 172.8, 138.4, 130.2, 129.5, 127.9, 59.0, 55.2, 55.1, 54.2, 48.8, 40.4, 40.2, 38.3, 33.5, 26.6, 26.5, 24.7, 24.6, 21.7, 17.1 and 16.0. Diastereoisomer B (28mg, 8%), <sup>1</sup>H-NMR; δ (methanol-d<sub>4</sub>), 7.95 (0.4H, s), 7.84 (0.6H, s), 7.26-7.21 (5H, m), 5.13 (0.4H, m), 5.04 (0.6H, m), 4.73-4.66 (0.4H, m), 4.62-4.56 (0.6H, m), 4.42-4.36 (0.4H, m), 3.89-3.78 (0.6H, m), 3.18-2.61 (3H, bm), 1.77-1.44 (10H, m), 1.29-1.11 (3H, m), 1.00-0.87 (7H, m); <sup>13</sup>C-NMR; δ(methanol-d<sub>4</sub>), 172.7, 138.0, 130.4, 129.5, 127.9, 79.6, 59.0, 53.3, 49.6, 39.9, 38.8, 38.4, 33.5, 33.4, 27.1, 26.7, 24.7, 24.6, 24.3, 24.1, 22.1, 21.9, 16.2 and 15.2.

## Example 3

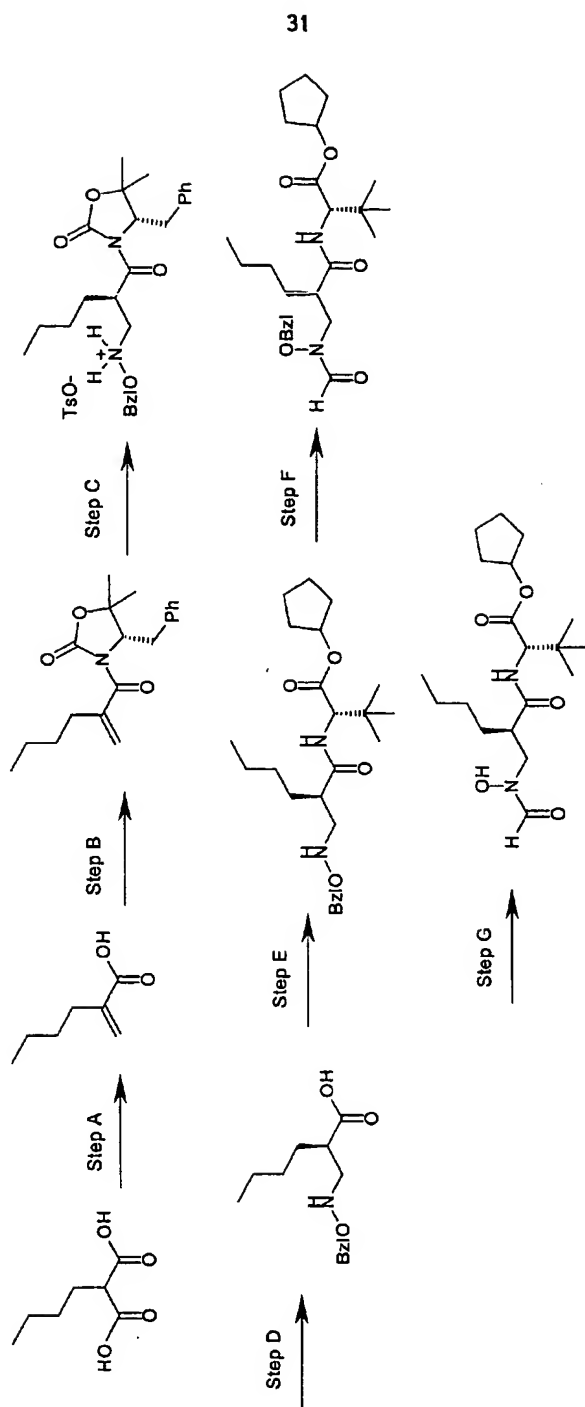
2S-{2R-[(Formyl-hydroxy-amino)-methyl]-hexanoylamino}-3,3-dimethyl butyric acid  
cyclopentyl ester

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The title compound was prepared as outlined in Scheme 3 and is described in detail  
below:

Scheme 3



Reagents and conditions: A. piperidine, HCHO, EtOH, 80°C, o/n; B.  $\text{H}_2\text{NOBzl}$ , room temp., o/n then pTsOH, EtOAc; C.  $\text{H}_2$ , Pd/C, EtOH; D.  $\text{H}_2$ , Pd/C, EtOH; E.  $\text{H}_2$ , Pd/C, EtOH; F.  $\text{H}_2$ , Pd/C, EtOH; G.  $\text{H}_2$ , Pd/C, EtOH.

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## Step A: 2-Butyl acrylic acid

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To a solution of n-butyldmalonic acid (17.2g, 107mmol) in ethanol (200ml) was added piperidine (12.76ml, 129mmol) and 37% aq. formaldehyde (40.3 ml, 538mmol). The solution was heated to 80°C during which time a precipitate appeared and then gradually redissolved over 1 hour. The reaction mixture was stirred at 80°C overnight then cooled to room temperature. The solvents were removed under reduced pressure and the residue was dissolved in ethyl acetate (200ml), washed successively with 1M hydrochloric acid and brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated to give the title compound as a clear oil (13.37g, 97%). <sup>1</sup>H-NMR; δ (CDCl<sub>3</sub>), 6.29 (1H, s), 5.65 (1H, s), 2.34-2.28 (2H, m), 1.54-1.26 (4H, m) and 0.94 (3H, t, J=7.1Hz).

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## Step B: 4S-Benzyl-3-(2-butyl-acryloyl)-5,5-dimethyl-oxazolidin-2-one

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2-Butyl acrylic acid (21.5g, 168mmol) was dissolved in dry THF (500ml) and cooled to -78°C under a blanket of argon. Triethylamine (30ml, 218mmol) and pivaloyl chloride (21ml, 168mmol) were added at such a rate that the temperature remained below -60°C. The mixture was stirred at -78°C for 30 minutes, warmed to room temperature for 2 hours and finally cooled back to -78°C.

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In a separate flask, 4S-benzyl-5,5-dimethyl-oxazolidin-2-one was dissolved in dry THF (500ml) and cooled to -78°C under a blanket of argon. n-Butyllithium (2.4M solution in hexanes, 83ml, 200mmol) was added slowly and the mixture was stirred for 30 minutes at room temperature. The resulting anion was transferred via a cannula into the original reaction vessel. The mixture was allowed to warm to room temperature and stirred overnight at room temperature. The reaction was quenched with 1M potassium hydrogen carbonate (200ml) and the solvents were removed under reduced pressure. The residue was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure to an orange oil. TLC

analysis revealed the presence of unreacted chiral auxiliary in addition to the required product. A portion of the material (30g) was dissolved in dichloromethane and flushed through a silica pad to give pure title compound as a yellow oil (25.3g).  
<sup>1</sup>H-NMR;δ (CDCl<sub>3</sub>), 7.31-7.19 (5H, m), 5.41 (2H, s), 4.51 (1H, dd, J=9.7, 4.2Hz), 3.32 (1H, dd, J=14.2, 4.2Hz), 2.82 (1H, dd, J=14.2, 9.7Hz), 2.40-2.34 (2H, m), 1.48-1.32 (4H, m), 1.43 (3H, s), 1.27 (3H, s) and 0.91 (3H, t, J=7.1Hz). Some chiral auxiliary was recovered by flushing the silica pad with methanol.

Step C: 4S-Benzyl-3-[2-(benzyloxyamino-methyl)-hexanoyl]-5,5-dimethyl-oxazolidin-2-one (p-toluenesulfonic acid salt)

4S-Benzyl-3-(2-butyl-acryloyl)-5,5-dimethyl-oxazolidin-2-one (19.8g, 62.8mmol) was mixed with O-benzylhydroxylamine (15.4g, 126mmol) and stirred overnight at room temperature. The mixture was dissolved in ethyl acetate and the solution was washed with 1M hydrochloric acid, 1M sodium carbonate and brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure to a pale yellow oil (25.3g) which was shown by NMR and HPLC analysis to contain 4S-Benzyl-3-[2-(benzyloxyamino-methyl)-hexanoyl]-5,5-dimethyl-oxazolidin-2-one (ca. 82% d.e.) along with a trace of starting material. The product was combined with another batch (26.9g, 76% d.e.) and dissolved in ethyl acetate (200ml). p-Toluenesulfonic acid (22.7g, 119mmol) was added and the mixture was cooled to 0°C. The title compound was obtained as a white crystalline solid by seeding and scratching. Yield: 25.2g, (34%, single diastereoisomer). A second crop (14.7g, 20%, single diastereoisomer) was also obtained. <sup>1</sup>H-NMR;δ (CDCl<sub>3</sub>), 7.89 (2H, d, J=8.2Hz), 7.37-7.12 (10H, m), 7.02 (2H, d, J=6.9Hz), 5.28-5.19 (2H, m), 4.55 (1H, m), 4.23 (1H, m), 3.93 (1H, m), 3.58 (1H, m), 2.58 (1H, m), 2.35 (3H, s), 1.67-1.51 (2H, m), 1.29-1.16 (4H, m), 1.25 (3H, s), 1.11 (3H, s) and 0.80-0.75 (3H, m).

Step D: 2R-Benzyl-3-[2-(benzyloxyamino-methyl)-hexanoic acid

4S-Benzyl-3-[2R-(benzyloxyamino-methyl)-hexanoyl]-5,5-dimethyl-oxazolidin-2-one

p-toluenesulfonic acid salt (25.2g, 40.2mmol) was partitioned between ethyl acetate and 1M sodium carbonate. The organic phase was dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure. The residual oil was dissolved in THF (150ml) and water (50ml) and cooled to 0°C and treated with lithium hydroxide (1.86g, 44.2mmol). The solution was stirred for 30 minutes at 0°C, then overnight at room temperature. The reaction was acidified to pH4 with 1M citric acid and the solvents were removed. The residue was partitioned between dichloromethane and 1M sodium carbonate. The basic aqueous layer was acidified to pH4 with 1M citric acid and extracted three times with ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated to provide the title compound as a colourless oil (7.4g, 73%). <sup>1</sup>H-NMR;δ (CDCl<sub>3</sub>), 8.42 (2H, br s), 7.34-7.25 (5H, m), 4.76-4.66 (2H, m), 3.20-3.01 (2H, m), 2.73 (1H, m), 1.70-1.44 (2H, m), 1.34-1.22 (4H, m) and 0.92-0.86 (3H, m).

Step E: 2S-[2R-(Benzyloxyamino-methyl)-hexanoylamino]-3,3-dimethyl butyric acid cyclopentyl ester

2R-Benzyloxyamino-methyl)-hexanoic acid (1.99g, 7.93mmol) was dissolved in DMF (50ml) and the solution was cooled to 0°. EDC (874mg, 4.56mmol) and HOBt (62mg, 0.46mmol) were added and the mixture was stirred for 15 minutes. *tert*-Leucine cyclopentyl ester (1.0g, 5.02mmol) was added and the reaction was allowed to warm to room temperature and stirred overnight. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate, washed successively with 1M hydrochloric acid, saturated sodium hydrogen carbonate and brine, dried and filtered. The solvent was removed to leave a yellow oil which was purified by flash chromatography (silica gel, 20% ethyl acetate in hexane) to afford the title compound (964mg, 28%) <sup>1</sup>H-NMR;δ (CDCl<sub>3</sub>), 7.36-7.29 (5H, m), 6.62 (1H, br d, J=9.2Hz), 5.69 (1H, br s), 5.22-5.18 (1H, m), 4.73 (2H, s), 4.42 (1H, d, J=9.4Hz), 3.11-3.04 (2H,m), 2.51 (1H, m), 1.87-1.59 (10H, m), 1.30-1.23 (4H, m), 0.97 (9H, s) and 0.87 (3H, t, J=6.7Hz).

Step F: 2S-{2R-[(Benzyloxy-formyl-amino)-methyl]-hexanoylamino}-3,3-dimethyl butyric acid cyclopentyl ester

2S-[2R-(Benzyloxyamino-methyl)-hexanoylamino]-3,3-dimethyl butyric acid cyclopentyl ester (947mg, 2.19mmol) was dissolved in dry THF (40ml) and treated with 1-formyl-benzotriazole (354mg, 2.41mmol). The reaction was stirred overnight at room temperature. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate and washed with 1M sodium carbonate solution and brine. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated to dryness under reduced pressure. The desired product was obtained by flash chromatography (silica gel, eluting with 25% ethyl acetate in hexane). Yield: 814mg (81%). <sup>1</sup>H-NMR; δ (CDCl<sub>3</sub>, rotamers), 8.13 (0.7H, br s), 7.88 (0.3H, br s), 7.37 (5H, br s), 6.02 (1H, br d, J=9.1Hz), 5.18 (1H, m), 4.96 (1H, br s), 4.76 (1H, br s), 4.35 (1H, d, J=9.2Hz), 3.74 (2H, br s), 2.53 (1H, m), 1.87-1.59 (10H, m), 1.28-1.23 (4H, m), 0.96-0.84 (3H, m) and 0.93 (9H, s).

Step G: 2S-{2R-[(Formyl-hydroxy-amino)-methyl]-hexanoylamino}-3,3-dimethyl butyric acid cyclopentyl ester

2S-{2R-[(Benzyloxy-formyl-amino)-methyl]-hexanoylamino}-3,3-dimethyl butyric acid cyclopentyl ester (780mg, 1.69mmol) was dissolved in ethanol (40ml) and placed under a blanket of argon. 10% palladium on charcoal (80mg) was added and the mixture was stirred vigorously as hydrogen gas was bubbled through the system. After 30 minutes the suspension was placed under a balloon of hydrogen and stirred overnight at room temperature. The flask was purged with argon before removing the catalyst by filtration. The filtrate was concentrated under reduced pressure to provide the title compound as a white foam (458mg, 73%). <sup>1</sup>H-NMR; δ (CD<sub>3</sub>OD, rotamers), 0.84 (0.4H, s), 7.82 (0.6H, s), 5.19-5.15 (1H, m), 4.27 (1H, s), 3.82-3.61 (1.4H, m), 3.45-3.37 (0.6H, m), 3.10-2.88 (1H, m), 1.89-1.31 (14H, m), 1.01 (3.6H, s), 0.99 (5.4H, s) and 0.92-0.87 (3H, m). <sup>13</sup>C-NMR; δ (CDCl<sub>3</sub>, rotamers), 172.8, 171.1, 78.7, 78.4, 60.4, 60.2, 51.7, 48.0, 46.2, 44.8, 34.9, 34.7, 32.7, 32.6, 30.1,

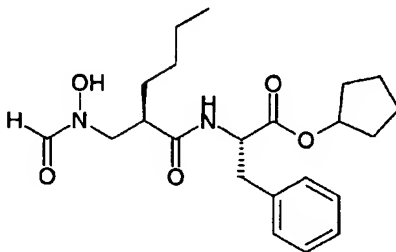
29.9, 29.3, 29.2, 26.6, 23.6, 22.6 and 13.8. IR (reflection disc)  $\nu_{\max}$  2978, 1740, 1690, 1549, 1379, 1237, 1171, 984, 882  $\text{cm}^{-1}$ . LRMS: 393 (M+Na), 369 (M-H).

The compounds of Examples 4-6 were prepared by the method of Example 3, by using the appropriate amino acid derivative instead of *tert*-leucine cyclopentyl ester in Step E:

#### Example 4

2S-{2R-[(Formyl-hydroxy-amino)-methyl]-hexanoylamino}-3-phenyl-propionic acid cyclo-pentyl ester

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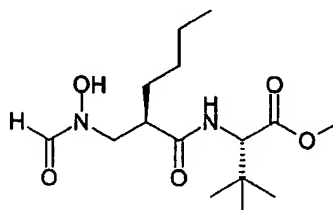
$^1\text{H-NMR}$ ;  $\delta$  ( $\text{CD}_3\text{OD}$  rotamers), 8.13 (0.4H, s), 7.81 (0.6H, s), 7.36-6.92 (5H, m), 5.11-5.07 (1H, m), 4.61 (1H, t,  $J=7.6\text{Hz}$ ), 3.65-3.46 (1H, m), 3.42-3.30 (1H, m), 3.19-2.92 (2H, m), 2.89-2.77 (0.6H, m), 2.74-2.51 (0.4H, m), 1.98-1.29 (14H, m) and 0.89-0.81 (3H, m).  $^{13}\text{C-NMR}$ ;  $\delta$  ( $\text{CD}_3\text{OD}$  rotamers), 173.0, 171.6, 136.2, 129.8, 129.6, 129.1, 129.0, 127.7, 127.5, 79.6, 79.0, 53.9, 53.6, 51.9, 48.5, 46.4, 45.0, 38.6, 38.0, 33.0, 32.9, 30.3, 30.2, 29.6, 29.5, 24.0, 23.0 and 14.2. IR (reflection disc);  $\nu_{\max}$  3325, 2958, 1731, 1663, 1532, 1443, 1367, 1280, 1199, 1104, 1079, 1032, 885, 749 and 699  $\text{cm}^{-1}$ . LRMS; +ve ion 427 (M+Na); -ve ion 403 (M-1).



## Example 5

2S-{2R-[(Formyl-hydroxy-amino)-methyl]-hexanoylamino}-3,3-dimethyl butyric acid methyl ester

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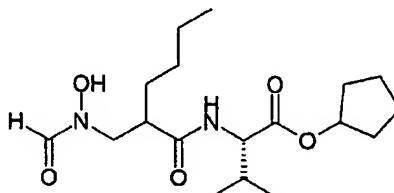


m.p. 63.5-64.5°C. <sup>1</sup>H-NMR; δ (CD<sub>3</sub>OD, rotamers), 8.24 (0.3H, s), 7.82 (0.7H, s), 4.33 (1H, s), 3.82-3.58 (1.3H, m), 3.70 (3H, s), 3.45-3.37 (0.7H, m), 3.11-3.01 (0.7H, m), 2.95-2.83 (0.3H, m), 1.55-1.20 (6H, m), 1.00 (3H, s), 0.99 (6H, s) and 0.93-0.88 (3H, m). <sup>13</sup>C-NMR; δ (CD<sub>3</sub>OD), 176.6, 173.2, 62.7, 53.9, 52.5, 45.4, 35.3, 31.6, 30.6, 27.6, 24.1 and 14.7. IR (reflection disc); ν<sub>max</sub> 3318, 2955, 1738, 1661, 1642, 1549, 1530, 1465, 1443, 1352, 1216, 1165, 1104, 1040, 1008 and 879 cm<sup>-1</sup>. LRMS; +ve ion 339 (M+Na), -ve ion 315 (M-H).

## Example 6

2S-{2R-[(Formyl-hydroxy-amino)-methyl]-hexanoylamino}-3-methyl butyric acid cyclo-pentyl ester

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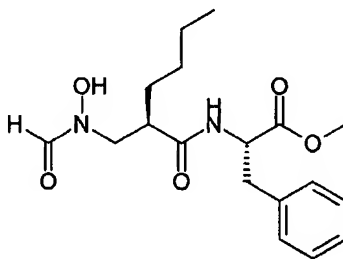
Pale yellow oil.  $^1\text{H-NMR}$ ;  $\delta$  ( $\text{CD}_3\text{OD}$ , rotamers), 8.25 (0.4H, s), 7.82 (0.6H, s), 5.19-5.15 (1H, m), 4.24 (1H, d,  $J=6.3$  Hz), 3.81-3.62 (1.4H, m), 3.49-3.38 (0.6H, m), 3.01-2.92 (0.6H, m), 2.81-2.75 (0.4H, m), 2.17-2.00 (1H, m), 1.90-1.34 (14H, m) and 0.95-0.88 (9H, m).  $^{13}\text{C-NMR}$ ;  $\delta$  ( $\text{CD}_3\text{OD}$ ), 176.6, 173.2, 159.8, 79.7, 60.0, 53.9, 45.8, 45.6, 34.0, 32.0, 31.5, 30.7, 25.0, 24.1, 19.9, 19.1 and 14.7. LRMS; +ve ion 379 ( $\text{M}+\text{Na}$ ), -ve ion 355 ( $\text{M}-\text{H}$ ).

The compounds of Example 7-10 were prepared by the method of Example 3 by parallel synthesis, using the appropriate amino acid derivative instead of *tert*-leucine cyclopentyl ester in Step E. The products were purified by preparative HPLC:

#### Example 7

2S-{2R-[(Formyl-hydroxy-amino)-methyl]-hexanoylamino}-3-phenyl-propionic acid methyl ester

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LRMS; +ve ion 373 ( $\text{M}+\text{Na}$ ), -ve ion 349 ( $\text{M}-\text{H}$ ).

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## Example 8

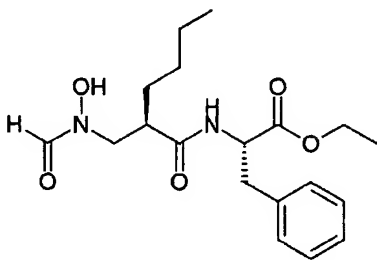
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2S-{2R-[(Formyl-hydroxy-amino)-methyl]-hexanoylamino}-3-phenyl-propionic acid  
ethyl ester

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LRMS; +ve ion 387 (M+Na), -ve ion 363 (M-H).

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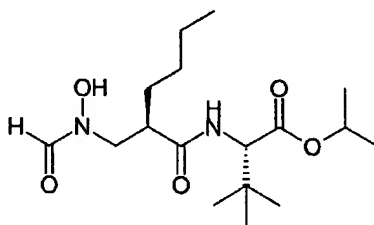
## Example 9

2S-{2R-[(Formyl-hydroxy-amino)-methyl]-hexanoylamino}-3,3-dimethyl butyric acid  
*iso*-propyl ester

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LRMS; +ve ion 367 (M+Na), -ve ion 343 (M-H)

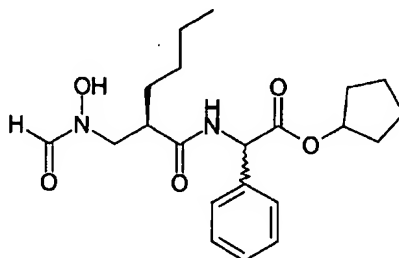
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## Example 10

2R (or S)-{2R-[(Formyl-hydroxy-amino)-methyl]-hexanoylamino}-2-phenyl acetic acid  
cyclopentyl ester

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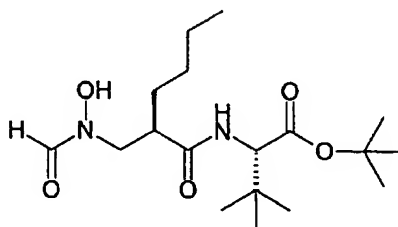
LRMS; +ve ion 413 (M+Na), 391 (M+H), -ve ion 389 (M-H)

Example 11 was prepared by the method of Example 3, by using the appropriate  
amino acid derivative instead of *tert*-leucine cyclopentyl ester in step E:

## Example 11

2S-{2R-[(Formyl-hydroxy-amino)-methyl]-hexanoylamino}-3,3-dimethyl-butyric acid  
*tert*-butyl ester

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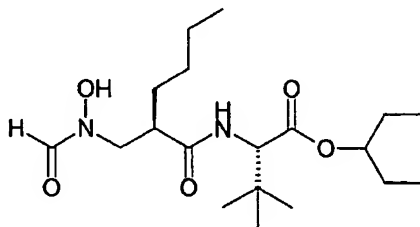
m.p. 76.1-78.2°C. <sup>1</sup>H-NMR; δ CDCl<sub>3</sub>, rotamers), 8.37 (0.4H, s), 7.80 (0.6H, s), 6.42  
(0.4H, d, J=9.3Hz), 6.29 (0.6H, d, J=9.5Hz), 4.33 (1H, d J=9.5Hz), 3.98 (0.4H, dd,

J=14.6, 7.3Hz), 3.85 (0.6H, dd, J=14.1, 9.6Hz), 3.64 (0.4H, dd, J=14.6, 3.5Hz), 3.45 (0.6H, dd, J=14.1, 4.2Hz), 2.85-2.75 (0.6H, m), 2.73-2.66 (0.4H, m), 1.67-1.19 (6H, m), 1.47 (9H, s), 0.99 (3H, s), 0.94 (6H, s) and 0.90-0.85 (3H, m). <sup>13</sup>C-NMR;  $\delta$  (CDCl<sub>3</sub>, rotamers) 176.3, 173.1, 170.9, 82.5, 61.2, 61.0, 52.1, 48.4, 46.7, 45.3, 35.0, 30.5, 30.4, 29.7, 29.6, 28.4, 27.0, 22.9 and 14.3. IR (reflection disc);  $\nu_{\max}$  3405, 2967, 1708, 1680, 1653, 1524, 1474, 1369, 1285, 1238 and 1173 cm<sup>-1</sup>. LRMS; +ve ion 381 [M+Na], -ve ion 357 [M-1].

The compounds of Examples 12 and 13 were prepared by the method of Example 3 by parallel synthesis, using the appropriate amino acid derivative instead of *tert* leucine cyclopentyl ester in Step E. The products were purified by preparative HPLC:

#### Example 12

2S-{2R-[(Formyl-hydroxy-amino)-methyl]-hexanoylamino}-3,3-dimethyl-butyric acid 1-ethyl-propyl ester

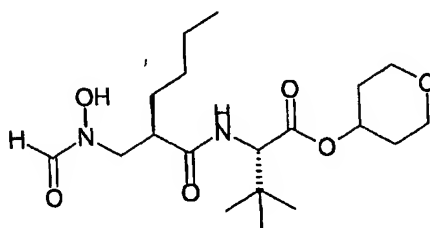


LRMS; +ve ion 373 [M+1], 395 [M+Na], -ve ion 371 [M-1].

**Example 13**

2S-{2R-[(Formyl-hydroxy-amino)-methyl]-hexanoylamino}-3,3-dimethyl-butyrlic acid  
tetrahydro-pyran-4-yl ester

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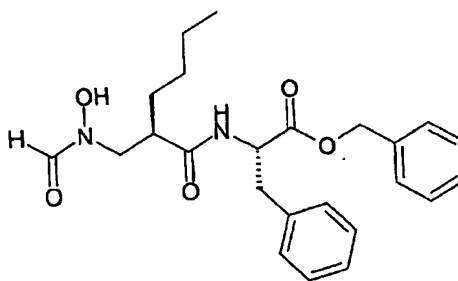
LRMS; +ve ion 387 [M+1], 409 [M+Na], -ve ion 385 [M-1].

The compounds of Examples 14 and 15 were prepared from 2R-(*tert*-butoxyamino-methyl)-hexanoic acid and the appropriate amino acid derivative by analogy with methods described for Example 3:

**Example 14**

2S-{2R-[(Formyl-hydroxy-amino)-methyl]-hexanoylamino}-3-phenyl-propionic acid  
benzyl ester

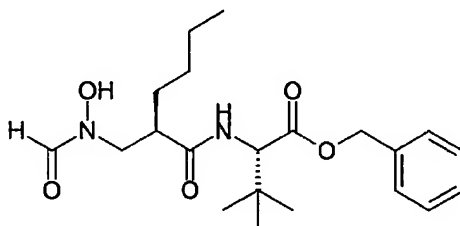
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<sup>1</sup>H-NMR; δ (CDCl<sub>3</sub>, rotamers) 8.33 (0.4H, s), 7.79 (0.6H, s), 7.37-7.21 (8H, m), 7.01-6.98 (2H, m), 6.24-6.15 (1H, m), 5.21-5.07 (2H, m), 4.94-4.84 (1H, m), 3.91 (0.4H, dd, J=14.7, 7.4Hz), 3.77 (0.6H, dd, J=14.3, 9.7Hz), 3.55 (0.4H, dd, J=14.5, 3.4Hz), 3.43 (0.6H, dd, J=14.2, 4.4Hz), 3.25-2.98 (2H, m), 2.71-2.64 (0.6H, m), 2.52-2.51 (0.4H, m), 1.56-1.25 (6H, m) and 0.84 (3H, br.s). <sup>13</sup>C-NMR; δ (CDCl<sub>3</sub>, rotamers) 157.7, 172.5, 171.2, 135.5, 135.3, 135.0, 134.8, 129.3, 129.2, 128.7, 128.6, 127.4, 127.2, 67.7, 67.4, 53.4, 50.8, 48.0, 46.1, 44.6, 38.0, 37.6, 29.9, 29.8, 29.1, 29.0, 22.5 and 13.7. LRMS; +ve ion 427 [M+1], 449 [M+Na].

### Example 15

2S-[2R-[(Formyl-hydroxy-amino)-methyl]-hexanoylamino]-3,3-dimethyl-butyrac benzyl ester

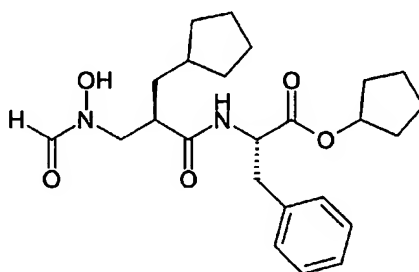


<sup>1</sup>H-NMR; δ (CDCl<sub>3</sub>, rotamers) 8.35 (0.2H, s), 7.74 (0.8H, s), 7.35 (5H, s), 6.50 (1H, d, J=9.3Hz), 5.21-5.15 (2H, m), 4.45 (1H, d, J=9.3Hz), 3.98 (0.2H, dd, J=14.6, 7.4Hz), 3.82 (0.8H, dd, J=14.1, 9.8Hz), 3.62 (0.2H, dd, J=14.7, 3.5Hz), 3.42 (0.8H, dd, J=14.1, 3.9Hz), 2.88-2.74 (0.8H, m), 2.71-2.63 (0.2H, m), 1.66-1.16 (6H, m), and 0.98-0.83 (12H, m). <sup>13</sup>C-NMR; δ (CDCl<sub>3</sub>, rotamers) 176.4, 173.4, 171.6, 135.6, 129.0, 128.9, 67.7, 67.4, 60.9, 60.7, 52.6, 48.3, 46.5, 45.0, 35.3, 35.1, 30.5, 30.3, 29.6, 29.5, 27.0, 26.9, 22.9 and 14.3. LRMS; +ve ion 393 [M+1], 415 [M+Na], -ve ion 391 [M-1].

Example 16 was prepared from 3-benzyloxyamino-2R-cyclopentylmethyl-propionic acid and phenylalanine cyclopentyl ester by analogy with methods described in patent number WO 99/39704:

### Example 16

2S-[2R-Cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionylamino]-3-phenyl-propionic acid cyclopentyl ester



m.p. 76.8-78.5°C. <sup>1</sup>H-NMR; δ CDCl<sub>3</sub>, rotamers) 8.34 (0.3H, s), 7.78 (0.7H, s), 7.34-7.09 (5H, m), 6.38-6.33 (1H, m), 5.24-5.19 (0.4H, m), 5.15-5.11 (0.6H, m), 4.83-4.71 (1H, m), 3.91(0.4H, dd, J=14.6, 7.4Hz), 3.76 (0.6H, dd, J=14.1, 9.5Hz), 3.55 (0.4H, dd, J=14.6, 3.4Hz), 3.42 (0.6H, dd, J=14.1, 4.3Hz), 3.23-2.92 (2H, m), 2.82-2.73 (0.7H, m), 2.58-2.56 (0.3H, m), 1.87-1.27 (17H, m) and 1.05-1.03 (2H, m). <sup>13</sup>C-NMR; δ (CDCl<sub>3</sub>, rotamers) 176.0, 173.1, 171.7, 171.5, 136.2, 136.1, 129.8, 129.6, 129.1, 128.9, 127.7, 127.5, 79.6, 79.0, 53.9, 53.6, 52.4, 48.8, 45.7, 44.4, 38.6, 38.0, 37.9, 37.7, 36.9, 36.8, 33.4, 33.3, 33.0, 32.9, 32.8, 32.7, 25.6, 25.5 and 24.0. IR (reflection disc); V<sub>max</sub> 3329, 2946, 2864, 1732, 1682, 1644, 1525, 1445, 1345, 1252, 1196 and 881 cm<sup>-1</sup>. LRMS; +ve ion 431 [M+1], -ve ion 429 [M-1].



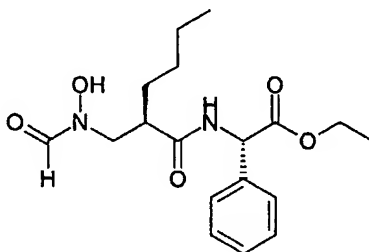
## Examples 17-28

Further compounds useful in accordance with the invention are those specifically named and characterised in International patent application WO 99/41232, as follows:

**Example 17**

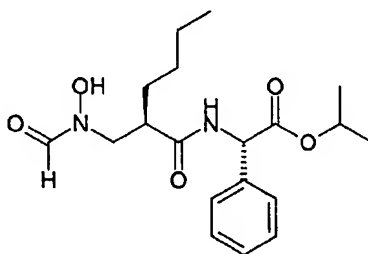
2S-{2R-[(Formyl-hydroxy-amino)-methyl]-hexanoylamino}-2-phenyl acetic acid ethyl ester (Example 10 of WO 99/41232.)

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**Example 18**

S-{2R-[(Formyl-hydroxy-amino)-methyl]-hexanoylamino}-2-phenyl acetic acid *iso*-propyl ester (Example 11 of WO 99/41232.)

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**Example 19**

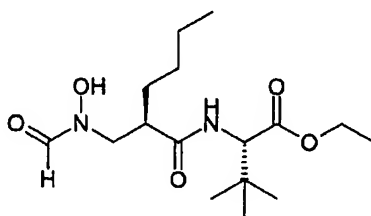
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2S-{2R-[(Formyl-hydroxy-amino)-methyl]-hexanoylamino}-3,3-dimethyl butyric acid ethyl ester (Example 12 of WO 99/41232.)

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**Example 20**

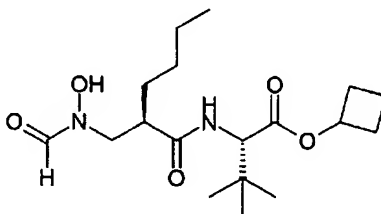
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2S-{2R-[(Formyl-hydroxy-amino)-methyl]-hexanoylamino}-3,3-dimethyl butyric acid cyclobutyl ester (Example 14 of WO 99/41232.)

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**Example 21**

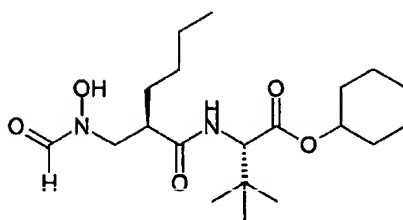
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2S-{2R-[(Formyl-hydroxy-amino)-methyl]-hexanoylamino}-3,3-dimethyl butyric acid cyclohexyl ester (Example 15 of WO 99/41232.)

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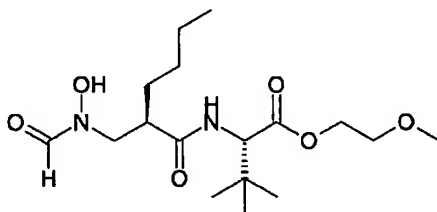
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**Example 22**

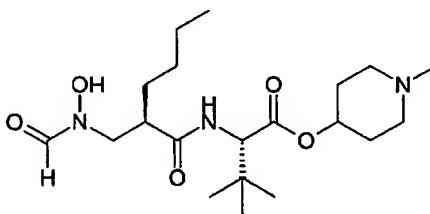
2S-{2R-[(Formyl-hydroxy-amino)-methyl]-hexanoylamino}-3,3-dimethyl butyric acid  
2-methoxy-ethyl ester (Example 16 of WO 99/41232.)

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**Example 23**

2S-{2R-[(Formyl-hydroxy-amino)-methyl]-hexanoylamino}-3,3-dimethyl butyric acid  
1-methyl-piperidin-4-yl ester (Example 17 of WO 99/41232.)

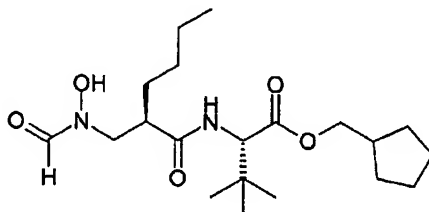
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**Example 24**

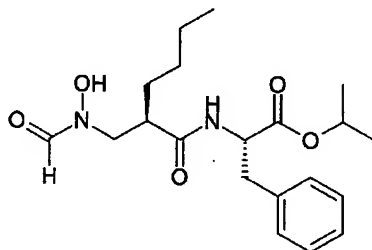
2S-{2R-[(Formyl-hydroxy-amino)-methyl]-hexanoylamino}-3,3-dimethyl butyric acid  
cyclopentylmethyl ester (Example 18 of WO 99/41232.)

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**Example 25**

2S-{2R-[(Formyl-hydroxy-amino)-methyl]-hexanoylamino}-3-phenyl-propionic acid  
*iso*-propyl ester (Example 19 of WO 99/41232.)

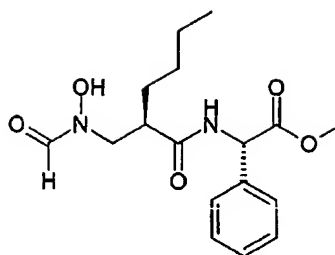
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**Example 26**

S-{2R-[(Formyl-hydroxy-amino)-methyl]-hexanoylamino}-2-phenyl acetic acid methyl  
ester (Example 20 of WO 99/41232.)

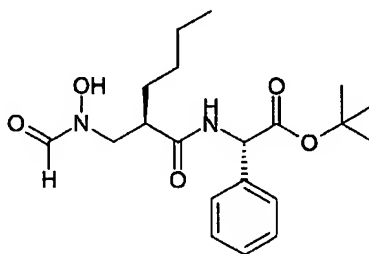
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**Example 27**

S-(2R-[(Formyl-hydroxy-amino)-methyl]-hexanoylamino)-2-phenyl acetic acid *tert*-butyl ester (Example 21 of WO 99/41232.)

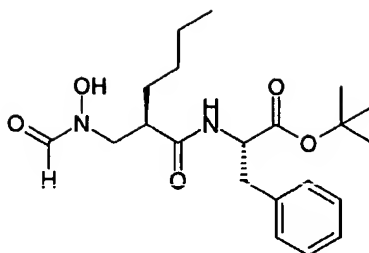
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**Example 28**

2S-(2R-[(Formyl-hydroxy-amino)-methyl]-hexanoylamino)-3-phenyl-propionic acid *tert*-butyl ester (Example 22 of WO 99/41232.)

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### Biological Example

#### Inhibition of Leukotriene Synthesis by Rat Basophilic Leukaemia Cells

The rat basophilic leukaemia cell line RBL-1 was obtained from ATCC or ECACC and cultured in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% foetal bovine serum, non-essential amino acids, sodium pyruvate, penicillin, streptomycin and 2mM glutamine, at 37°C in an atmosphere of 5% CO<sub>2</sub> in air, as recommended by the culture collection.

RBL-1 cells were harvested during log growth, washed and resuspended in Hanks Balanced Salt Solution, without calcium chloride and magnesium chloride, supplemented with 10% foetal bovine serum and penicillin, streptomycin, and 2mM glutamine and adjusted to a final cell concentration of  $1.25 \times 10^5$  cells/ml. Cells incubated in the presence of the appropriate concentration of inhibitor or vehicle for 4.75 hours at 37°C. Cells then transferred to ice for 15 minutes. Cells washed by centrifugation and resuspension in pre-chilled Phosphate Buffered Saline, with calcium chloride and magnesium chloride, supplemented with the appropriate concentration of test sample. After the PBS wash, cells resuspended at a final cell concentration of equivalent to  $2.35 \times 10^9$  cell/ml in PBS/sample buffer. Cells transferred to a microfuge tube on ice prior to ionophore stimulation.

Treated cells then exposed to 10µM A23187 for 15 minutes at 37°C. Cells

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transferred to ice, thereby stopping the reaction. Cell free supernatant harvested by centrifugation. The levels of leukotriene B<sub>4</sub> then determined in the cell free supernatant using the Leukotriene B<sub>4</sub> [<sup>3</sup>H] assay system from Amersham Pharmacia Biotech.

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Using this methodology the IC<sub>50</sub> value for the compound of example 4 was estimated as 0.7nM and for Kelatorphan as 350nM.

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## Claims

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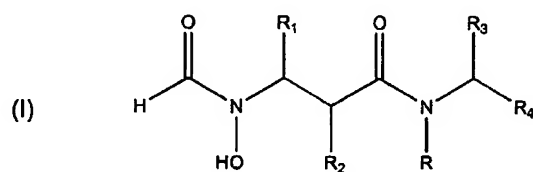
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## Claims

1. A method of treatment of mammals suffering diseases responsive to inhibition of intracellular leukotriene- $A_4$  hydrolase activity, comprising administering to the mammal suffering such disease an amount of a compound of general formula (I) or a pharmaceutically acceptable salt hydrate or solvate thereof sufficient to inhibit such activity:



wherein

R is hydrogen or (C<sub>1</sub>-C<sub>8</sub>)alkyl;

R<sub>1</sub> is hydrogen;

(C<sub>1</sub>-C<sub>8</sub>)alkyl;

(C<sub>2</sub>-C<sub>8</sub>)alkenyl;

phenyl or substituted phenyl;

phenyl (C<sub>1</sub>-C<sub>8</sub>)alkyl or substituted phenyl(C<sub>1</sub>-C<sub>8</sub>)alkyl;

phenyl (C<sub>2</sub>-C<sub>8</sub>)alkenyl or substituted phenyl(C<sub>2</sub>-C<sub>8</sub>)alkenyl

heterocyclyl or substituted heterocyclyl;

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heterocyclyl(C<sub>1</sub>-C<sub>8</sub>)alkyl or substituted heterocyclyl(C<sub>1</sub>-C<sub>8</sub>)alkyl;

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a group BSO<sub>n</sub>A- wherein n is 0, 1 or 2 and B is hydrogen or a (C<sub>1</sub>-C<sub>8</sub>) alkyl, phenyl, substituted phenyl, heterocyclyl substituted heterocyclyl, (C<sub>1</sub>-C<sub>8</sub>)acyl, phenacyl or substituted phenacyl group, and A represents (C<sub>1</sub>-C<sub>8</sub>)alkylene;

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amino(C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>1</sub>-C<sub>8</sub>)alkylamino(C<sub>1</sub>-C<sub>8</sub>)alkyl, di(C<sub>1</sub>-C<sub>8</sub>)alkylamino(C<sub>1</sub>-C<sub>8</sub>)alkyl, hydroxy(C<sub>1</sub>-C<sub>8</sub>)alkyl, mercapto(C<sub>1</sub>-C<sub>8</sub>)alkyl or carboxy(C<sub>1</sub>-C<sub>8</sub>) alkyl wherein the amino-, hydroxy-, mercapto- or carboxyl-group are optionally protected or the carboxyl- group amidated;

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lower alkyl substituted by carbamoyl, mono(lower alkyl)carbamoyl, di(lower alkyl)carbamoyl, di(lower alkyl)amino, or carboxy-lower alkanoylamino; or

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a cycloalkyl, cycloalkenyl or non-aromatic heterocyclic ring containing up to 3 heteroatoms, any of which may be (i) substituted by one or more substituents selected from C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>2</sub>-C<sub>8</sub> alkenyl, halo, cyano ( -CN), -CO<sub>2</sub>H, -CO<sub>2</sub>R, -CONH<sub>2</sub>, -CONHR, -CON(R)<sub>2</sub>, -OH, -OR, oxo-, -SH, -SR, -NHCOR, and -NHCO<sub>2</sub>R wherein R is C<sub>1</sub>-C<sub>8</sub> alkyl or benzyl and/or (ii) fused to a cycloalkyl or heterocyclic ring;

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R<sub>2</sub> is a C<sub>1</sub>-C<sub>12</sub> alkyl,  
C<sub>2</sub>-C<sub>12</sub> alkenyl,  
C<sub>2</sub>-C<sub>12</sub> alkynyl,  
phenyl(C<sub>1</sub>-C<sub>8</sub> alkyl)-,  
heteroaryl(C<sub>1</sub>-C<sub>8</sub> alkyl)-,  
phenyl(C<sub>2</sub>-C<sub>8</sub> alkenyl)-,  
heteroaryl(C<sub>2</sub>-C<sub>8</sub> alkenyl)-,  
phenyl(C<sub>2</sub>-C<sub>8</sub> alkynyl)-,  
heteroaryl(C<sub>2</sub>-C<sub>8</sub> alkynyl)-,  
cycloalkyl(C<sub>1</sub>-C<sub>8</sub> alkyl)-,

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cycloalkyl(C<sub>2</sub>-C<sub>6</sub> alkenyl)-,  
cycloalkyl(C<sub>2</sub>-C<sub>6</sub> alkynyl)-,  
10 cycloalkenyl(C<sub>1</sub>-C<sub>6</sub> alkyl)-,  
cycloalkenyl(C<sub>2</sub>-C<sub>6</sub> alkenyl)-,  
cycloalkenyl(C<sub>2</sub>-C<sub>6</sub> alkynyl)-,  
phenyl(C<sub>1</sub>-C<sub>6</sub> alkyl)O(C<sub>1</sub>-C<sub>6</sub> alkyl)-, or  
15 heteroaryl(C<sub>1</sub>-C<sub>6</sub> alkyl)O(C<sub>1</sub>-C<sub>6</sub> alkyl)- group,  
any one of which may be optionally substituted by

C<sub>1</sub>-C<sub>6</sub> alkyl,  
20 C<sub>1</sub>-C<sub>6</sub> alkoxy,  
halo,  
cyano (-CN),  
phenyl or heteroaryl, or  
25 phenyl or heteroaryl substituted by  
C<sub>1</sub>-C<sub>6</sub> alkyl,  
C<sub>1</sub>-C<sub>6</sub> alkoxy,  
30 halo, or  
cyano (-CN);

35 R<sub>3</sub> is the characterising group of a natural or non-natural  $\alpha$  amino acid in which  
any functional groups may be protected; and

40 R<sub>4</sub> is an ester or thioester group.

2. The use of a compound of formula (I) as defined in claim 1 in the preparation  
of a composition for treatment of mammals suffering diseases responsive to  
45 inhibition of intracellular leukotriene-A<sub>4</sub> hydrolase activity.

3. A method as claimed in claim 1 or the use as claimed in claim 2 wherein the  
stereochemical configuration of the carbon atom carrying the groups R<sub>3</sub> and R<sub>4</sub> is S.  
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4. A method as claimed in claim 1, the use or claim 2, or a method or use as claimed in claim 3, wherein  $R_1$  is:

hydrogen, methyl, ethyl, n-propyl, n-butyl, isobutyl, cyclopropylmethyl, allyl, phenylpropyl, phenylprop-2-enyl, thienylsulphanylmethyl, thienylsulphinylmethyl, or thienylsulphonylmethyl; or

$C_1$ - $C_4$  alkyl, eg methyl, ethyl n-propyl or n-butyl, substituted by a phthalimido, 1,2-dimethyl-3,5-dioxo-1,2,4-triazolidin-4-yl, 3-methyl-2,5-dioxo-1-imidazolidinyl, 3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl, 2-methyl-3,5-dioxo-1,2,4-oxadiazol-4-yl, 3-methyl-2,4,5-trioxo-1-imidazolidinyl, 2,5-dioxo-3-phenyl-1-imidazolidinyl, 2-oxo-1-pyrrolidinyl, 2,5-dioxo-1-pyrrolidinyl or 2,6-dioxopiperidinyl, 5,5-dimethyl-2,4-dioxo-3-oxazolidinyl, hexahydro-1,3-dioxopyrazolo[1,2,a][1,2,4]-triazol-2-yl, or a naphththalimido (ie 1,3-dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl), 1,3-dihydro-1-oxo-2H-benz[f]isoindol-2-yl, 1,3-dihydro-1,3-dioxo-2H-pyrrolo[3,4-b]quinolin-2-yl, or 2,3-dihydro-1,3-dioxo-1H-benz[d,e]isoquinolin-2-yl group; or

cyclohexyl, cyclooctyl, cycloheptyl, cyclopentyl, cyclobutyl, cyclopropyl, tetrahydropyranyl or morpholinyl.

5. A method as claimed in claim 1, the use or claim 2, or a method or use as claimed in claim 3, wherein  $R_1$  is hydrogen, cyclopropylmethyl, n-propyl, or allyl.

6. A method as claimed in claim 1, the use or claim 2, or a method or use as claimed in claim 3, wherein  $R_2$  is:

$C_1$ - $C_{12}$  alkyl,  $C_3$ - $C_8$  alkenyl or  $C_3$ - $C_8$  alkynyl;

phenyl( $C_1$ - $C_6$  alkyl)-, phenyl( $C_3$ - $C_8$  alkenyl)- or phenyl( $C_3$ - $C_8$  alkynyl)- optionally substituted in the phenyl ring;

heteroaryl(C<sub>1</sub>-C<sub>8</sub> alkyl)-, heteroaryl(C<sub>3</sub>-C<sub>8</sub> alkenyl)- or heteroaryl(C<sub>3</sub>-C<sub>8</sub> alkynyl)- optionally substituted in the heteroaryl ring;

4-phenylphenyl(C<sub>1</sub>-C<sub>8</sub> alkyl)-, 4-phenylphenyl(C<sub>3</sub>-C<sub>8</sub> alkenyl)-, 4-phenylphenyl(C<sub>3</sub>-C<sub>8</sub> alkynyl)-, 4-heteroarylphenyl(C<sub>1</sub>-C<sub>8</sub> alkyl)-, 4-heteroarylphenyl(C<sub>3</sub>-C<sub>8</sub> alkenyl)-, 4-heteroarylphenyl(C<sub>3</sub>-C<sub>8</sub> alkynyl)-, optionally substituted in the terminal phenyl or heteroaryl ring; or

phenoxy(C<sub>1</sub>-C<sub>8</sub> alkyl)- or heteroaryloxy(C<sub>1</sub>-C<sub>8</sub> alkyl)- optionally substituted in the phenyl or heteroaryl ring.

7. A method as claimed in claim 1, the use or claim 2, or a method or use as claimed in claim 3, wherein R<sub>2</sub> is: methyl, ethyl, n- or iso-propyl, n-, iso- or tert-butyl, n-pentyl, n-hexyl, n-heptyl, n-nonyl, n-decyl, prop-2-yn-1-yl, 3-phenylprop-2-yn-1-yl, 3-(2-chlorophenyl)prop-2-yn-1-yl, benzyl phenylpropyl, 4-chlorophenylpropyl, 4-methylphenylpropyl, 4-methoxyphenylpropyl, phenoxybutyl, 3-(4-pyridylphenyl)propyl-, 3-(4-(4-pyridyl)phenyl)prop-2-yn-1-yl, 3-(4-phenylphenyl)propyl-, 3-(4-phenyl)phenyl)prop-2-yn-1-yl or 3-[(4-chlorophenyl)phenyl]propyl-.

8. A method as claimed in claim 1, the use or claim 2, or a method or use as claimed in claim 3, wherein R<sub>2</sub> is benzyl, n-butyl, iso-butyl, n-hexyl, or cyclopentylmethyl.

9. A method as claimed in claim 1, the use or claim 2, or a method or use as claimed in claim 3, wherein R<sub>3</sub> is C<sub>1</sub>-C<sub>8</sub> alkyl, phenyl, 2-, 3-, or 4-pyridyl, 2- or 3-thienyl, 2-, 3-, or 4-hydroxyphenyl, 2-, 3-, or 4-methoxyphenyl, 2-, 3-, or 4-pyridylmethyl, benzyl, 2-, 3-, or 4-hydroxybenzyl, 2-, 3-, or 4-benzyloxybenzyl, 2-, 3-, or 4-C<sub>1</sub>-C<sub>8</sub> alkoxybenzyl, or benzyloxy(C<sub>1</sub>-C<sub>8</sub>alkyl)-.

10. A method as claimed in claim 1, the use or claim 2, or a method or use as

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claimed in claim 3, wherein  $R_3$  is the characterising group of a natural  $\alpha$  amino acid, in which any functional group may be protected, any amino group may be acylated and any carboxyl group present may be amidated.

11. A method as claimed in claim 1, the use or claim 2, or a method or use as claimed in claim 3, wherein  $R_3$  is a group  $-[Alk]_nR_8$  where Alk is a  $(C_1-C_6)$ alkyl or  $(C_2-C_6)$ alkenyl group optionally interrupted by one or more -O-, or -S- atoms or -N( $R_7$ )- groups [where  $R_7$  is a hydrogen atom or a  $(C_1-C_6)$ alkyl group], n is 0 or 1, and  $R_8$  is an optionally substituted cycloalkyl or cycloalkenyl group.

12. A method as claimed in claim 1, the use or claim 2, or a method or use as claimed in claim 3, wherein  $R_3$  is a benzyl group substituted in the phenyl ring by a group of formula  $-OCH_2COR_8$  where  $R_8$  is hydroxyl, amino,  $(C_1-C_6)$ alkoxy, phenyl( $C_1-C_6$ )alkoxy,  $(C_1-C_6)$ alkylamino, di( $(C_1-C_6)$ alkyl)amino, phenyl( $C_1-C_6$ )alkylamino, the residue of an amino acid or acid halide, ester or amide derivative thereof, said residue being linked via an amide bond, said amino acid being selected from glycine,  $\alpha$  or  $\beta$  alanine, valine, leucine, isoleucine, phenylalanine, tyrosine, tryptophan, serine, threonine, cysteine, methionine, asparagine, glutamine, lysine, histidine, arginine, glutamic acid, and aspartic acid.

13. A method as claimed in claim 1, the use or claim 2, or a method or use as claimed in claim 3, wherein  $R_3$  is a heterocyclic( $C_1-C_6$ )alkyl group, either being unsubstituted or mono- or di-substituted in the heterocyclic ring with halo, nitro, carboxy,  $(C_1-C_6)$ alkoxy, cyano,  $(C_1-C_6)$ alkanoyl, trifluoromethyl  $(C_1-C_6)$ alkyl, hydroxy, formyl, amino,  $(C_1-C_6)$ alkylamino, di- $(C_1-C_6)$ alkylamino, mercapto,  $(C_1-C_6)$ alkylthio, hydroxy( $C_1-C_6$ )alkyl, mercapto( $C_1-C_6$ )alkyl or  $(C_1-C_6)$ alkylphenylmethyl.

14. A method as claimed in claim 1, the use or claim 2, or a method or use as claimed in claim 3, wherein  $R_3$  is a group  $-CR_aR_bR_c$  in which:  
each of  $R_a$ ,  $R_b$  and  $R_c$  is independently hydrogen,  $(C_1-C_6)$ alkyl,  $(C_2-C_6)$ alkenyl,  $(C_2-C_6)$ alkynyl, phenyl( $C_1-C_6$ )alkyl,  $(C_3-C_6)$ cycloalkyl; or

$R_c$  is hydrogen and  $R_a$  and  $R_b$  are independently phenyl or heteroaryl such as pyridyl; or

$R_c$  is hydrogen,  $(C_1-C_6)$ alkyl,  $(C_2-C_6)$ alkenyl,  $(C_2-C_6)$ alkynyl, phenyl $(C_1-C_6)$ alkyl, or  $(C_3-C_8)$ cycloalkyl, and  $R_a$  and  $R_b$  together with the carbon atom to which they are attached form a 3 to 8 membered cycloalkyl or a 5- to 6-membered heterocyclic ring; or

$R_a$ ,  $R_b$  and  $R_c$  together with the carbon atom to which they are attached form a tricyclic ring (for example adamantyl); or

$R_a$  and  $R_b$  are each independently  $(C_1-C_6)$ alkyl,  $(C_2-C_6)$ alkenyl,  $(C_2-C_6)$ alkynyl, phenyl $(C_1-C_6)$ alkyl, or a group as defined for  $R_c$  below other than hydrogen, or  $R_a$  and  $R_b$  together with the carbon atom to which they are attached form a cycloalkyl or heterocyclic ring, and  $R_c$  is hydrogen, -OH, -SH, halogen, -CN, -CO<sub>2</sub>H,  $(C_1-C_4)$ perfluoroalkyl, -CH<sub>2</sub>OH, -CO<sub>2</sub> $(C_1-C_6)$ alkyl, -O $(C_1-C_6)$ alkyl, -O $(C_2-C_6)$ alkenyl, -S $(C_1-C_6)$ alkyl, -SO $(C_1-C_6)$ alkyl, -SO<sub>2</sub> $(C_1-C_6)$ alkyl, -S $(C_2-C_6)$ alkenyl, -SO $(C_2-C_6)$ alkenyl, -SO<sub>2</sub> $(C_2-C_6)$ alkenyl or a group -Q-W wherein Q represents a bond or -O-, -S-, -SO- or -SO<sub>2</sub>- and W represents a phenyl, phenylalkyl,  $(C_3-C_8)$ cycloalkyl,  $(C_3-C_8)$ cycloalkylalkyl,  $(C_4-C_8)$ cycloalkenyl,  $(C_4-C_8)$ cycloalkenylalkyl, heteroaryl or heteroarylalkyl group, which group W may optionally be substituted by one or more substituents independently selected from, hydroxyl, halogen, -CN, -CO<sub>2</sub>H, -CO<sub>2</sub> $(C_1-C_6)$ alkyl, -CONH<sub>2</sub>, -CONH $(C_1-C_6)$ alkyl, -CONH $(C_1-C_6)$ alkyl<sub>2</sub>, -CHO, -CH<sub>2</sub>OH,  $(C_1-C_4)$ perfluoroalkyl, -O $(C_1-C_6)$ alkyl, -S $(C_1-C_6)$ alkyl, -SO $(C_1-C_6)$ alkyl, -SO<sub>2</sub> $(C_1-C_6)$ alkyl, -NO<sub>2</sub>, -NH<sub>2</sub>, -NH $(C_1-C_6)$ alkyl, -N $((C_1-C_6)$ alkyl)<sub>2</sub>, -NHCO $(C_1-C_6)$ alkyl,  $(C_1-C_6)$ alkyl,  $(C_2-C_6)$ alkenyl,  $(C_2-C_6)$ alkynyl,  $(C_3-C_8)$ cycloalkyl,  $(C_4-C_8)$ cycloalkenyl, phenyl or benzyl.

15. A method as claimed in claim 1, the use or claim 2, or a method or use as claimed in claim 3, wherein  $R_3$  is phenyl, benzyl, tert-butoxymethyl, iso-propyl or iso-butyl.

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16. A method as claimed in claim 1, the use or claim 2, or a method or use as claimed in claim 3, wherein  $R_4$  is a group of formula  $-(C=O)OR_9$ ,  $-(C=O)SR_9$ ,  $-(C=S)SR_9$ , and  $-(C=S)OR_9$  wherein  $R_9$  is  $(C_1-C_6)$ alkyl,  $(C_2-C_6)$ alkenyl, cycloalkyl, cycloalkyl $(C_1-C_6)$ alkyl-, phenyl, heterocyclyl, phenyl $(C_1-C_6)$ alkyl-, heterocyclyl $(C_1-C_6)$ alkyl-,  $(C_1-C_6)$ alkoxy $(C_1-C_6)$ alkyl-, or  $(C_1-C_6)$ alkoxy $(C_1-C_6)$ alkoxy $(C_1-C_6)$ alkyl-, any of which may be substituted on a ring or non-ring carbon atom or on a ring heteroatom, if present.

17. A method as claimed in claim 1, the use or claim 2, or a method or use as claimed in claim 3, wherein  $R_4$  is a group of formula  $-(C=O)OR_9$  wherein  $R_9$  is methyl, ethyl, n- or iso-propyl, n-, sec- or tert-butyl, 1-ethyl-prop-1-yl, 1-methyl-prop-1-yl, 1-methyl-but-1-yl, cyclopentyl, cyclohexyl, allyl, phenyl, benzyl, 2-, 3- and 4-pyridylmethyl, N-methylpiperidin-4-yl, 1-methylcyclopent-1yl, adamantyl, tetrahydrofuran-3-yl or methoxyethyl.

18. A method as claimed in claim 1, the use or claim 2, or a method or use as claimed in claim 3, wherein  $R_4$  is a group of formula  $-(C=O)OR_9$  wherein  $R_9$  is benzyl, cyclopentyl, cyclohexyl or isopropyl.

19. A method as claimed in claim 1, the use or claim 2, or a method or use as claimed in claim 3, wherein  $R$  is hydrogen or methyl.

20. A method as claimed in claim 1, the use or claim 2, or a method or use as claimed in claim 3, wherein  $R$  is hydrogen;  $R_1$  is hydrogen, cyclopropylmethyl, n-propyl or allyl;  $R_2$  is benzyl, n-butyl, iso-butyl, n-hexyl or cyclopentylmethyl;  $R_3$  is phenyl, benzyl, tert-butoxymethyl, isopropyl or iso-butyl; and  $R_4$  is a group of formula  $-(C=O)OR_9$  wherein  $R_9$  is benzyl, cyclopentyl, cyclohexyl or isopropyl.

21. A method as claimed in claim 1, the use or claim 2, or a method or use as claimed in any of claims 3-20, wherein the disease is asthma, rheumatoid arthritis,



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osteoarthritis, multiple sclerosis, ulcerative colitis, contact or atopic dermatitis,  
psoriasis, inflammatory bowel disease or Crohn's disease.

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# INTERNATIONAL SEARCH REPORT

Int. Application No  
PCT/GB 00/00162

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/216 A61K31/223 A61K31/351 A61K31/445 A61K31/16  
A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	WO 99 41232 A (BRITISH BIOTECH PHARM ;AYSCOUGH ANDREW PAUL (GB); DRUMMOND ALAN HA) 19 August 1999 (1999-08-19) cited in the application the whole document	1-21
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents:

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Date of the actual completion of the international search

16 May 2000

Date of mailing of the international search report

23/05/2000

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# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/GB 00/00162

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FOURNIE-ZALUSKI M -C ET AL: "NEW BIDENTASES AS FULL INHIBITORS OF ENKEPHALIN-DEGRADING ENZYMES: SYNTHESIS AND ANALGESIS PROPERTIES" JOURNAL OF MEDICINAL CHEMISTRY, US, AMERICAN CHEMICAL SOCIETY. WASHINGTON, vol. 28, no. 9, 1 January 1985 (1985-01-01), pages 1158-1169, XP002019770 ISSN: 0022-2623 abstract; figure 3; table I ---	1-21
A	WO 94 10990 A (GALLOWAY WILLIAM ALAN ;BRITISH BIO TECHNOLOGY (GB); CRIMMIN MICHAEL) 26 May 1994 (1994-05-26) abstract page 9, last paragraph page 14, paragraph 1 - paragraph 2; claims 3,20,21 ---	1-21
A	WO 95 22966 A (SANOFI WINTHROP INC) 31 August 1995 (1995-08-31) cited in the application abstract; claims 1,9 ---	1-21
A	WO 95 19965 A (GLYCOMED INC) 27 July 1995 (1995-07-27) cited in the application abstract page 27, line 3 -page 30, line 31; claims 1,2,10 ---	1-21
A	PENNING ET AL: "Kelatorphan and related analogs: potent and selective inhibitors of leukotriene A4 hydrolase" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, GB, OXFORD, vol. 5, no. 21, 1995, pages 2517-2522, XP002103716 ISSN: 0960-894X cited in the application the whole document -----	1-21

# INTERNATIONAL SEARCH REPORT

international application No.

PCT/GB 00/00162

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1, 3-21  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claims 1, 3-21  
are directed to a method of treatment of the human/animal  
body, the search has been carried out and based on the alleged  
effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such  
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all  
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment  
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report  
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is  
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. Patent Application No  
PCT/GB 00/00162

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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